IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Kohji Funatsu, et al.
Serial No. 10/534,081 Group Art Unit 1614
Filed June 13, 2005 Examiner CORNET, JEAN P.
For : RECEPTOR FUNCTIONAL REGULATOR

TRANSLATOR'S DECLARATION

Honorable Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313

Sir:

I, Ritsuko Arimura, declare:

That I am well acquainted with both the Japanese and English languages;

That the attached document represents a true English translation of Japanese Patent Application No. 2003-016889 (filing date January 27, 2003); and

That I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this second day of March, 2010.

Ritsuko Arimura

Ritsuko Arimura

【Document】 Specification

【Title of the Invention】 Receptor Function Regulator

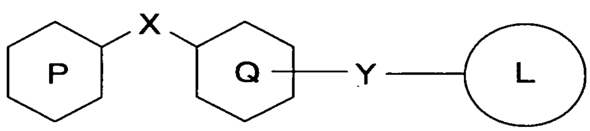
【What is Claimed is】

【Claim 1】 A GPR40 receptor function regulator comprising a compound having an aromatic ring and a group capable of releasing cation.

【Claim 2】 The regulator of claim 1, which comprises a carboxylic acid having an aromatic ring, or a derivative thereof.

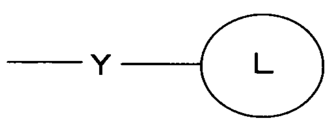
【Claim 3】 The regulator of claim 1, which comprises a carboxylic acid having two or more aromatic rings, or a derivative thereof.

【Claim 4】 The regulator of claim 1, which comprises a compound represented by the formula



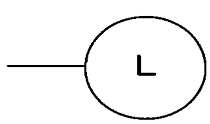
(I ')

wherein ring P is an aromatic ring optionally having substituent(s), ring Q is an aromatic ring optionally further having substituent(s) besides



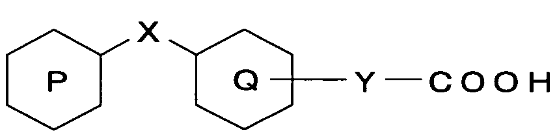
,

X and Y are each a spacer, and



is a group capable of releasing cation, or a salt thereof or a prodrug thereof.

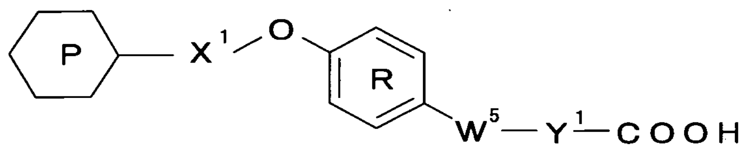
【Claim 5】 The regulator of claim 2, which comprises a compound represented by the formula



(I)

wherein ring P is an aromatic ring optionally having substituent(s), ring Q is an aromatic ring optionally further having substituent(s) besides -Y-COOH, X and Y are each a spacer, and -Y-COOH is substituted at any position on ring Q, or a salt thereof or a prodrug thereof.

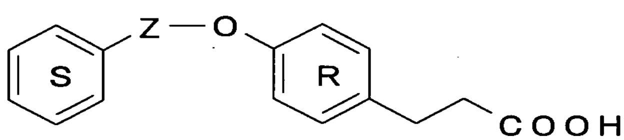
【Claim 6】 The regulator of claim 2, which comprises a compound represented by the formula



(I a)

wherein ring P is an aromatic ring optionally having substituent(s), ring R is a phenylene group optionally having substituent(s), X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, -O-, -N(R^6)-, -CO-N(R^7)- or -S-, R^6 and R^7 are each a C_{1-6} alkyl group, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s), or a salt thereof or a prodrug thereof.

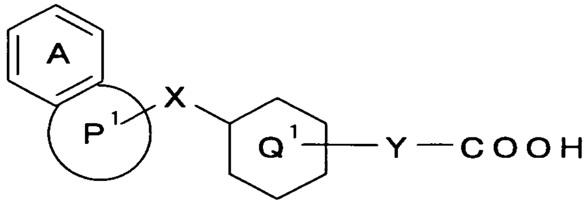
【Claim 7】 The regulator of claim 2, which comprises a compound represented by the formula



(I b)

wherein ring S is a benzene ring optionally having substituent(s), ring R is a phenylene group optionally having substituent(s), and Z is a chain formed by 4 linkages, or a salt thereof or a prodrug thereof.

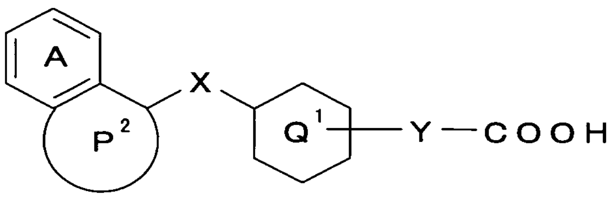
【Claim 8】 The regulator of claim 2, which comprises a compound represented by the formula



(II)

wherein ring A is a benzene ring optionally having substituent(s), ring P^1 is a ring optionally having substituent(s), ring Q^1 is an aromatic ring optionally further having substituent(s) besides -Y-COOH, X and Y are each a spacer, and -Y-COOH is substituted at any potition on ring Q^1, or a salt thereof or a prodrug thereof.

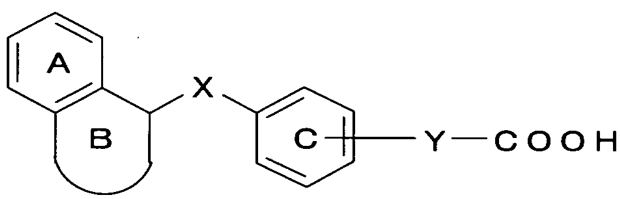
【Claim 9】 The regulator of claim 8, which comprises a compound represented by the formula



(IIa)

wherein ring P^2 is a ring optionally having substituent(s), and other symbols are as defined in claim 6, or a salt thereof or a prodrug thereof.

【Claim 10】 The regulator of claim 8, which comprises a compound represented by the formula



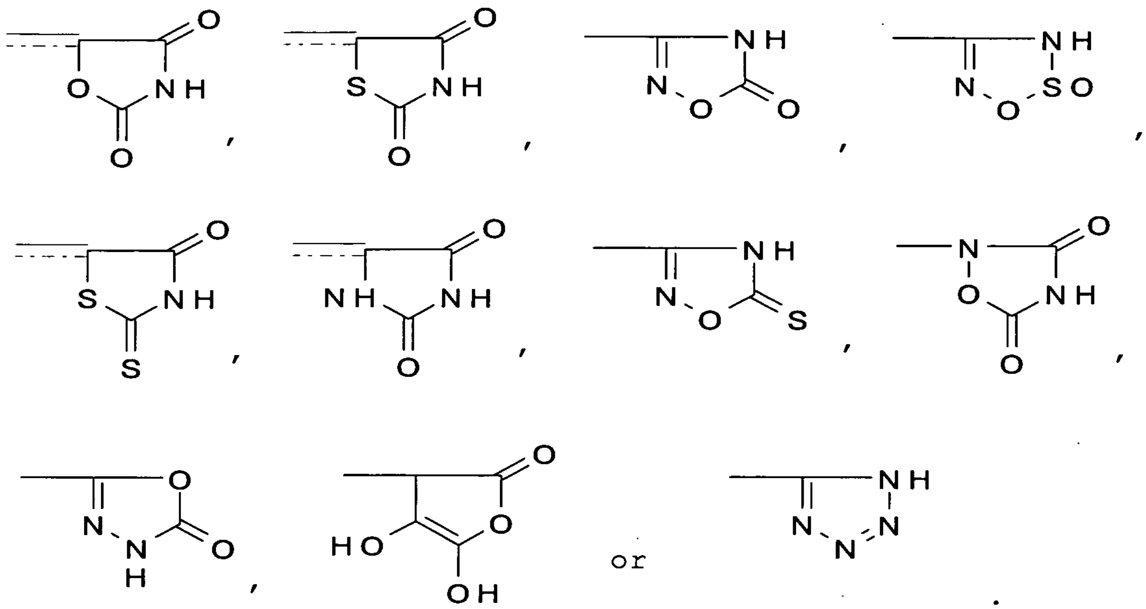
(IIb)

wherein ring A is a benzene ring optionally having substituent(s), ring B is a 5- to 7-membered ring optionally having substituent(s), ring C is a benzene ring optionally further having substituent(s) besides a -Y-COOH group, X and Y are each a spacer, and -Y-COOH is substituted at any position on ring C, or a salt thereof or a prodrug thereof.

【Claim 11】 The regulator of claim 1, wherein the group capable of releasing cation is (1) a 5-membered heterocyclic group capable of releasing cation, (2) a cyano group, (3) a carboxyl group, (4) a C_{2-7} alkoxycarbonyl group, (5) a C_{7-11} aryloxycarbonyl group, (6) a 5 or 6-membered heterocyclyl-oxycarbonyl group containing, besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and

a sulfur atom, (7) a sulfonic acid group, (8) a sulfamoyl group optionally mono-substituted by a C_{1-4} alkyl group, (9) a phosphonic acid group, (10) di-C_{1-4} alkoxyphosphoryl group, (11) a carbamoyl group optionally mono-substituted by a C_{1-4} alkyl group, (12) a C_{2-7} alkylsulfonylthiocarbamoyl group or (13) a trifluoromethanesulfonic acid amido group ($-NHSO_2CF_3$).

【Claim 12】 The regulator of claim 1, wherein the group capable of releasing cation is



【Claim 13】 The regulator of any one of claims 4 to 6, wherein ring P is a benzene ring optionally having substituent(s) or a non-basic aromatic heterocycle optionally having substituent(s).

【Claim 14】 The regulator of any one of claims 4 to 6, wherein ring P is a benzene ring optionally having substituent(s).

【Claim 15】 The regulator of any one of claims 4 to 6, wherein ring P is a benzene ring optionally having substituent(s) at the meta-position.

【Claim 16】 The regulator of any one of claims 4 to 6, wherein the substituent of ring P is a substituent having an aromatic ring.

【Claim 17】 The regulator of claim 16, wherein the substituent having an aromatic ring is a substituent represented by the

formula: R^1-E- (R^1 is an aromatic group optionally having substituent(s), and E is a bond or a spacer).

【Claim 18】 The regulator of claim 17, wherein -E- is a bond, -O-, $-CH_2-O-$, -CO-, -CONH- or $-N(R^2)-CH_2-$ (R^2 is a C_{1-6} alkyl group).

【Claim 19】 The regulator of claim 17, wherein -E- is a bond, -O- or $-CH_2-O-$.

【Claim 20】 The regulator of claim 17, wherein R^1 is (i) a phenyl group optionally having substituent(s) selected from the group consisting of a halogen atom and an optionally halogenated C_{1-6} alkyl or (ii) a 5- to 14-membered heterocyclic group containing, besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, which optionally has substituent(s) selected from an optionally halogenated C_{1-6} alkyl, a C_{6-14} aryl and a C_{6-14} aryl-C_{2-6} alkenyl, and E is a bond or $-(CH_2)m^1-W^1-(CH_2)m^2-$ (m^1 and m^2 are each an integer of 0 to 3, W^1 is -O-, $-N(R^2)-$ or $-CO-N(R^3)-$, and R^2 and R^3 are each a C_{1-6} alkyl group).

【Claim 21】 The regulator of claim 5, wherein ring Q is a benzene ring optionally having substituent(s).

【Claim 22】 The regulator of any one of claims 4, 5, 8, 9 and 10, wherein the spacer represented by X is

(i) $-X^1-W^2-X^2-$ (X^1 and X^2 are each a bond or a C_{1-6} alkylene group optionally having substituent(s), W^2 is -O-, $-N(R^4)-$, $-CO-N(R^5)-$ or -S-, and R^4 and R^5 are each a C_{1-6} alkyl group), or

(ii) $-W^3-X^3-W^4-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), W^3 and W^4 are each -O-, $-N(R^4)-$, $-CO-N(R^5)-$ or -S-, and R^4 and R^5 are each a C_{1-6} alkyl group).

【Claim 23】 The regulator of any one of claims 4, 5, 8, 9 and 10, wherein the spacer represented by X is $-X^1-O-X^2-$ (X^1 and X^2 are each a bond or a C_{1-6} alkylene group optionally having substituent(s)).

【Claim 24】 The regulator of any one of claims 4, 5, 8, 9 and 10, wherein the spacer represented by X is $-X^1-O-$ (X^1 is a bond or

a C_{1-6} alkylene group optionally having substituent(s)).

【Claim 25】 The regulator of claim 24, wherein X^1 is (i) a bond or (ii) a C_{1-6} alkylene group optionally having substituent(s) selected from a C_{1-6} alkyl and a C_{6-14} aryl.

【Claim 26】 The regulator of any one of claims 4, 5, 8, 9 and 10, wherein the spacer represented by X is

(i) a bond,

(ii) $-X^1-O-$ (X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s)),

(iii) $-N(R^4)-X^3-O-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), and R^4 is a C_{1-6} alkyl group),

(iv) $-S-X^3-O-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)),

(v) $-N(R^4)-X^3-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), and R^4 is a C_{1-6} alkyl group),

(vi) $-CO-N(R^5)-$ (R^5 is a C_{1-6} alkyl group),

(vii) $-X^3-S-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)), or

(viii) $-S-X^3-S-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)).

【Claim 27】 The regulator of any one of claims 4, 5, 8, 9 and 10, wherein Y is $-W^5-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, $-O-$, $-N(R^6)-$, $-CO-N(R^7)-$ or $-S-$, and R^6 and R^7 are each a C_{1-6} alkyl group).

【Claim 28】 The regulator of any one of claims 4, 5, 8, 9 and 10, wherein Y is a C_{1-6} alkylene group optionally having substituent(s).

【Claim 29】 The regulator of any one of claims 4, 5, 8, 9 and 10, wherein Y is an ethylene group optionally having substituent(s).

【Claim 30】 The regulator of any one of claims 4, 5, 8, 9 and 10, wherein Y is $-O-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)).

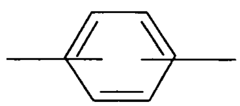
【Claim 31】 The regulator of any one of claims 4, 5, 8, 9 and 10,

wherein -Y-COOH is substituted at para-position on ring Q, ring Q′ or ring C.

【Claim 32】 The regulator of claim 7, wherein Z is

(1) a chain formed by 4 linkages selected from $-C(R^8)(R^{8'})-$, $-O-$, $-CO-$, $-N(R^{8''})-$ (R^8, $R^{8'}$ and $R^{8''}$ are each a C_{1-6} alkyl group) and $-S-$, or

(2) a chain formed by



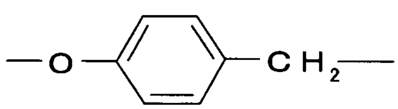
and 2 linkages selected from $-C(R^8)(R^{8'})-$, $-O-$, $-CO-$, $-N(R^{8''})-$ (R^8, $R^{8'}$ and $R^{8''}$ are each a C_{1-6} alkyl group) and $-S-$.

【Claim 33】 The regulator of claim 7, wherein Z is

(1) $-(CH_2)_4-$,

(2) $-O-(CH_2)_3-$,

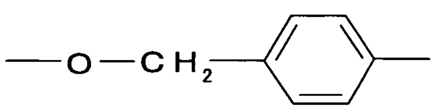
(3)



,

or

(4)



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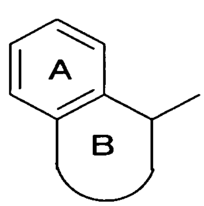
【Claim 34】 The regulator of claim 10, wherein B ring is a 5- to 7-membered ring optionally containing, besides carbon, a nitrogen atom, an oxygen atom or a sulfur atom, which optionally has substituent(s).

【Claim 35】 The regulator of claim 10, wherein



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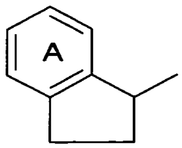
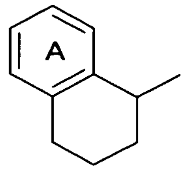
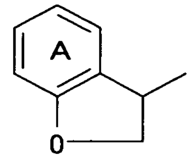
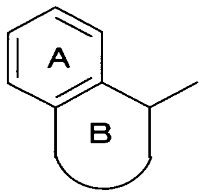
 ,  or  .

【Claim 36】 The regulator of claim 10, wherein



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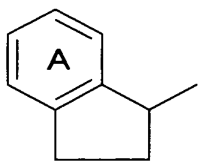
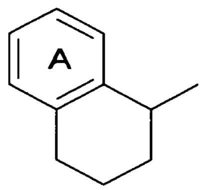
 or  .

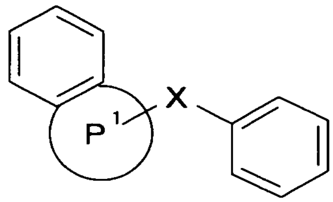
【Claim 37】 The regulator of claim 10, wherein the spacer represented by X is a methylene group optionally having substituent(s), -O- or -S-, and the spacer represented by Y is a C_{1-6} alkylene group optionally having substituent(s), $-N(R^6)-Y^1-$ (R^6 is a C_{1-6} alkyl group, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s)), $-O-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)) or $-S-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)).

【Claim 38】 The regulator of claim 1, which is an insulin secretion modulator or a pancreatic β cell protector.

【Claim 39】 The regulator of claim 1, which is an agent for the prophylaxis or treatment of diabetes, impaired glucose tolerance, ketosis, acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hyperlipidemia, genital disorder, skin disease, arthropathy, osteopenia, arteriosclerosis, thrombotic disease, dyspepsia, memory and learning disorder, obesity, hypoglycemia, hypertension, edema, insulin resistance syndrome, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, lipotoxicity or cancer.

【Claim 40】 A carboxylic acid having a skeleton represented by

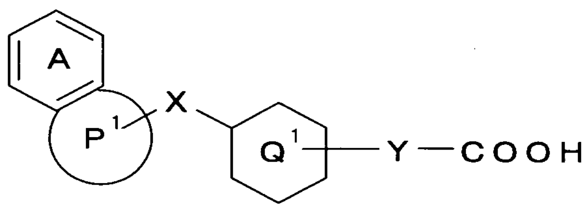
the formula



(III)

wherein X is a spacer, and ring P^1 is a ring optionally having substituent(s), or a derivative thereof.

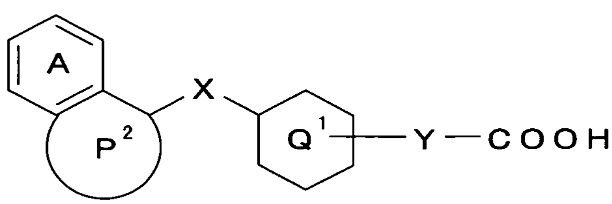
【Claim 41】 A compound represented by the formula



(II)

wherein ring A is a benzene ring optionally having substituent(s), ring P^1 is a ring optionally having substituent(s), ring Q^1 is an aromatic ring optionally further having substituent(s) besides -Y-COOH, X and Y are each a spacer, and -Y-COOH is substituted at any potition on ring Q^1, or a salt thereof or a prodrug thereof.

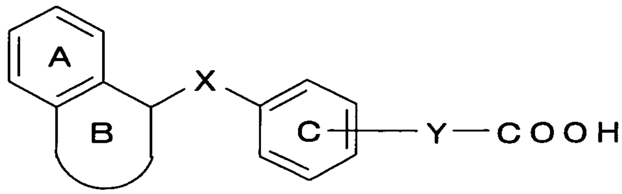
【Claim 42】 The compound of claim 41, which is a compound represented by the formula



(IIa)

wherein ring P^2 is a ring optionally having substituent(s), and other symbols are as defined in claim 35, or a salt thereof or a prodrug thereof.

【Claim 43】 The compound of claim 41, which is a compound represented by the formula

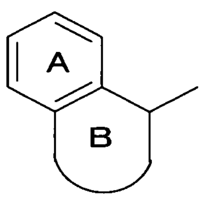


(IIb)

wherein ring A is a benzene ring optionally having substituent(s), ring B is a 5- to 7-membered ring optionally having substituent(s), ring C is a benzene ring optionally further having substituent(s) besides a -Y-COOH group, X and Y are each a spacer, and -Y-COOH is substituted at any position on ring C, or a salt thereof or a prodrug thereof.

【Claim 44】 The compound of claim 43, wherein B ring is a 5- to 7-membered ring optionally containing, besides carbon, a nitrogen atom, an oxygen atom or a sulfur atom, which optionally has substituent(s), or a salt thereof or a prodrug thereof.

【Claim 45】 The compound of claim 43, wherein



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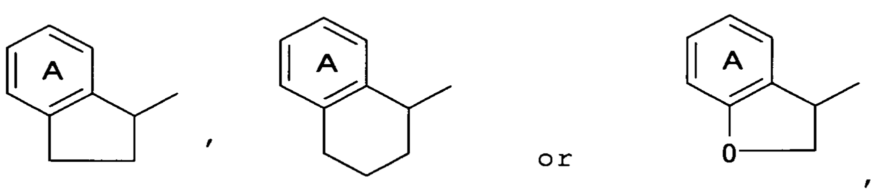
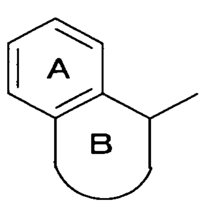


or a salt thereof or a prodrug thereof.

【Claim 46】 The compound of claim 43, wherein



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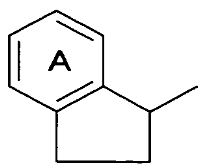
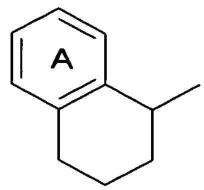
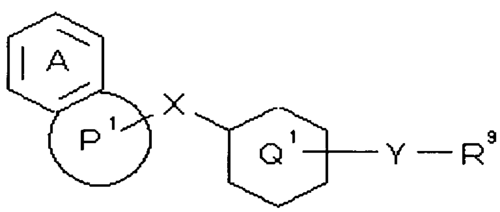
 or  ,

or a salt thereof or a prodrug thereof.

【Claim 47】 The compound of claim 43, wherein the spacer represented by X is a methylene group optionally having substituent(s), -O- or -S-, and the spacer represented by Y is a C_{1-6} alkylene group optionally having substituent(s), $-N(R^6)-Y^1-$ (R^6 is a C_{1-6} alkyl group, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s)), $-O-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)) or $-S-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)), or a salt thereof or a prodrug thereof.

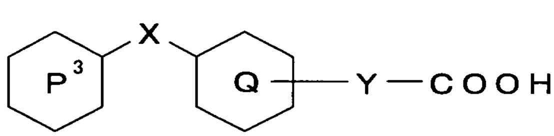
【Claim 48】 A production method of the compound of claim 41 or a salt thereof, wherein comprising subjecting a compound represented by the formula



(IIc)

wherein R^9 is a cyano group or $-COR^{10}$ (R^{10} is an optionally substituted amino group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aryloxy group or an optionally substituted C_{7-16} aralkyloxy group, and the other symbols are defined in claim 41, to hydrolysis.

【Claim 49】 A compound represented by the formula

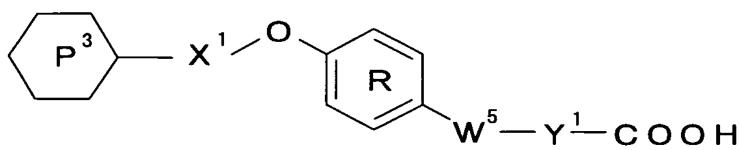


(IV)

wherein ring P^3 is an aromatic ring having substituent(s) having a benzene ring, ring Q is an aromatic ring optionally further having substituent(s) besides -Y-COOH, X and Y are each a spacer, and -Y-COOH is substituted at any position on

ring Q, or a salt thereof or a prodrug thereof, except (i) 2-ethoxy-4-[[2-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid, (ii) 2-ethoxy-4-[[3-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid, (iii) 2-ethoxy-4-[[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid, and (iv) 4-[[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid.

【Claim 50】 The compound of claim 49, which comprises a compound represented by the formula



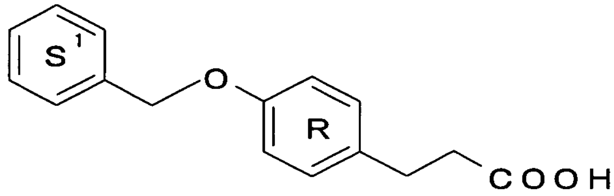
(IVa)

wherein ring P^3 is an aromatic ring having substituent(s) having a benzene ring, ring R is a phenylene group optionally having substituent(s), X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, -O-, -N(R^6)-, -CO-N(R^7)- or -S-, R^6 and R^7 are each a C_{1-6} alkyl group, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s), or a salt thereof or a prodrug thereof.

【Claim 51】 The compound of claim 50, wherein X^1 is a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s), or a salt thereof or a prodrug thereof.

【Claim 52】 The compound of claim 50, wherein X^1 is a methylene group optionally having substituent(s), W^5 is a bond, and Y^1 is an ethylene group optionally having substituent(s), or a salt thereof or a prodrug thereof.

【Claim 53】 The compound of claim 49, which is represented by the formula



(IVb)

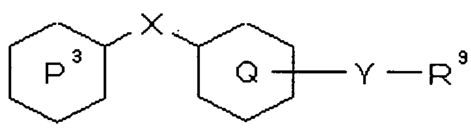
wherein ring S^1 is a benzene ring having substituent(s) having a benzene ring, and ring R is a phenylene group optionally having substituent(s), or a salt thereof or a prodrug thereof.

【Claim 54】 The compound of any one of claims 49 to 53, wherein the substituent(s) having a benzene ring is a substituent represented by the formula: R^{11}-E- (R^{11} is a phenyl group optionally having substituent(s), and E is a bond or a spacer), or a salt thereof or a prodrug thereof.

【Claim 55】 The compound of claim 54, wherein -E- is a bond, -O- or $-CH_2-O-$, or a salt thereof or a prodrug thereof.

【Claim 56】 The compound of claim 54, wherein R^{11} is a phenyl group optionally having substituent(s) selected from the group consisting of a halogen atom and an optionally halogenated C_{1-6} alkyl, or a salt thereof or a prodrug thereof.

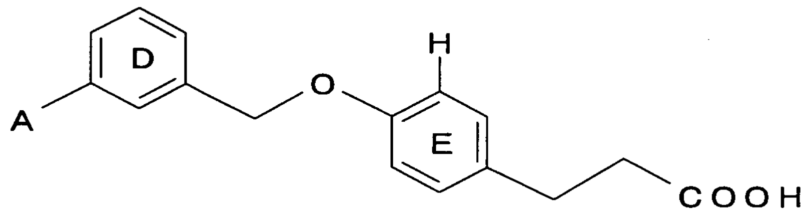
【Claim 57】 A production method of the compound of claim 49 or a salt thereof, wherein comprising subjecting a compound represented by the formula



(IVc)

wherein R^9 is a cyano group or $-COR^{10}$ (R^{10} is an optionally substituted amino group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aryloxy group or an optionally substituted C_{7-16} aralkyloxy group, and the other symbols are defined in claim 49, to hydrolysis.

【Claim 58】 A compound represented by the formula

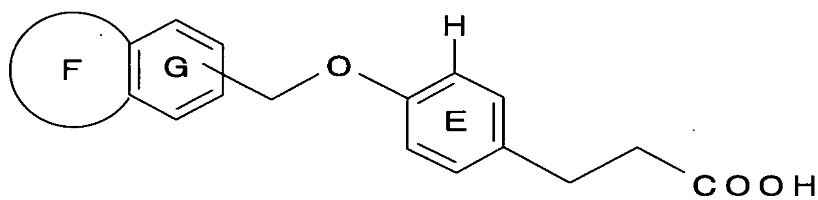


(A)

wherein A is a substituent (except a hydrogen atom and a chlorine atom), ring D is a benzene ring optionally further having, besides A, substituent(s) (except a nitro group and a hydroxy group), and ring E is a phenylene group optionally having substituent(s), or a salt thereof or a prodrug thereof, except 2-ethoxy-4-[[3-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid.

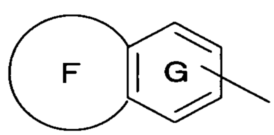
【Claim 59】 The compound of claim 58, wherein A is a bromine atom, or a salt thereof or a prodrug thereof.

【Claim 60】 A compound represented by the formula



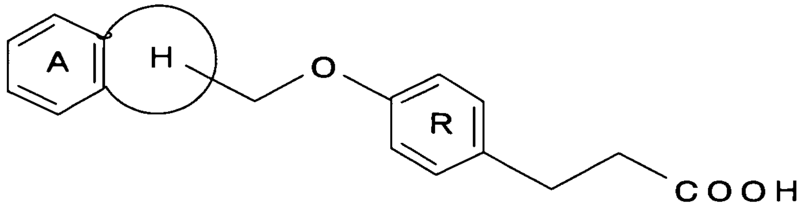
(B)

wherein ring F is a ring optionally having substituent(s), ring G is a benzene ring optionally having substituent(s), and ring E is a phenylene group optionally having substituent(s), provided that



is not an unsubstituted naphthyl group, an unsubstituted 1H-indazolyl group and a quinolyl group optionally having substituent(s), or a salt thereof or a prodrug thereof.

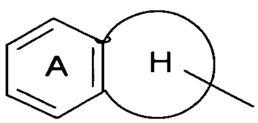
【Claim 61】 A compound represented by the formula



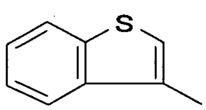
(C)

wherein ring A is a benzene ring optionally having substituent(s), ring H is a 5-membered ring optionally having substituent(s), and ring R is a phenylene group optionally having substituent(s), or a salt thereof or a prodrug thereof, except 3,5-dibromo-4-[(5-chlorobenzo[b]thiophen-3-yl)methoxy]benzenepropanoic acid, 4-(1H-benzotriazol-1-ylmethoxy)benzenepropanoic acid and 4-(1H-indol-3-ylmethoxy)benzenepropanoic acid.

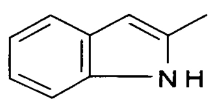
【Claim 62】 The compound of claim 61, wherein



is



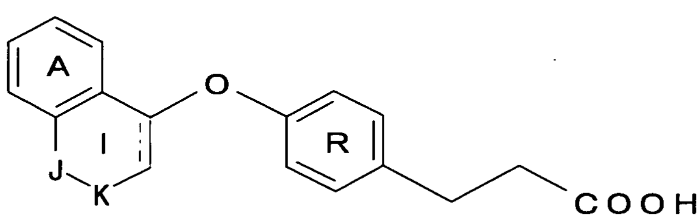
or



,

or a salt thereof or a prodrug thereof.

【Claim 63】 A compound represented by the formula

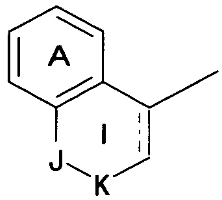


(D)

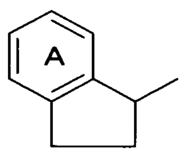
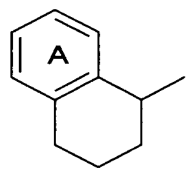
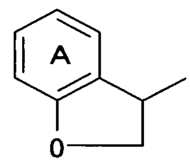
wherein ring A is a benzene ring optionally having substituent(s), J is -O-, -S-, $-CH_2-$ or $-NR^{12}-$ (R^{12} is a C_{1-6} alkyl group), K is a bond or a C_{1-3} alkylene group,

is a single bond or a double bond, ring R is a phenylene group optionally having substituent(s), and ring I optionally has substituent(s), or a salt thereof or a prodrug thereof.

【Claim 64】 The compound of claim 63, wherein



is

 ,  or  ,

the substituent of ring A is (i) a halogen atom, (ii) a C_{1-6} alkyl group, (iii) a C_{1-6} alkoxy group, (iv) a C_{6-14} aryl group optionally having substituent(s) selected from a halogen atom and a C_{1-6} alkyl, (v) a C_{6-14} aryloxy group or (vi) a C_{7-15} aralkyloxy group, and the substituent of ring R is a halogen atom, or a salt thereof or a prodrug thereof.

【Claim 65】 A pharamaceutical composition comprising the compound of any one of claims 40, 41, 49, 58, 60, 61 and 63 or a salt thereof or a prodrug thereof.

【Claim 66】 The pharamaceutical composition of claim 65, which is a GPR40 receptor function regulator.

【Claim 67】 The pharamaceutical composition of claim 65, which is An insulin secretion modulator or a pancreatic β cell protector.

【Claim 68】 The pharamaceutical composition of claim 65, which is an agent for the prophylaxis or treatment of diabetes, impaired glucose tolerance, ketosis, acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hyperlipidemia, genital disorder, skin disease, arthropathy, osteopenia, arteriosclerosis, thrombotic disease, dyspepsia, memory and learning disorder, obesity, hypoglycemia, hypertension, edema, insulin resistance syndrome, unstable diabetes, fatty atrophy, insulin allergy, insulinoma,

lipotoxicity or cancer.

【Claim 69】 A method of regulating a GPR40 receptor function, which comprises administering an effective amount of a carboxylic acid having an aromatic ring or a derivative thereof to a mammal.

【Claim 70】 Use of a carboxylic acid having an aromatic ring or a derivative thereof for the production of a GPR40 receptor function regulator.

【Detailed Description of the Invention】

【Technical Field to which the Invention Pertains】

The present invention relates to a GPR40 receptor function regulator comprising carboxylic acid having an aromatic ring or a derivative thereof and a novel compound having a GPR40 receptor function regulating action.

【Prior Art】

An amino acid sequence of GPR40 derived from human and DNA encoding same are described (Patent Document 1 and Non-Patent Document 1).

It is known that carboxylic acid having an aromatic ring and a derivative thereof have various physiological activities.

Alkanoic acid derivatives are known (Patent Document 2).

Isoxazole derivatives having an insulin secretagogue action and a hypoglycemic action, which are useful for the prophylaxis or treatment of diabetes and the like, are known (Patent Document 3).

Nitrogen-containing 5-membered heterocyclic compounds having a hypoglycemic action or a hypolipidemic action, which are useful for the prophylaxis or treatment of diabetes and the like, are known (Patent Document 4).

Alkoxyiminoalkanoic acid derivatives having a hypoglycemic action or a hypolipidemic action, which are useful for the prophylaxis or treatment of diabetes and the like, are known (Patent Document 5).

Oxyiminoalkanoic acid derivatives having a hypoglycemic action or a hypolipidemic action, which are useful for the prophylaxis or treatment of diabetes and the like, are known (Patent Document 6).

1,3-Azole derivatives having a retinoid-related receptor function regulating action, which are useful for the prophylaxis or treatment of diabetic complications and the like, are known (Patent Document 7).

Oxyiminoalkanoic acid derivatives having a hypoglycemic

action or a hypolipidemic action, which are useful for the prophylaxis or treatment of diabetes and the like, are known (Patent Document 8).

Oxazole derivatives having an insulin secretagogue action or a hypoglycemic action, which are useful for the prophylaxis or treatment of diabetes and the like, are known (Patent Document 9).

Benzofuran derivatives having a hypoglycemic and hypolipidemic action are known (Patent Document 10).

【Patent Document 1】
WO2000/22129

【Patent Document 2】
JP-A-2002-265457

【Patent Document 3】
JP-A-2002-212171

【Patent Document 4】
JP-A-2001-226350

【Patent Document 5】
JP-A-2001-199971

【Patent Document 6】
JP-A-2000-198772

【Patent Document 7】
JP-A-2000-80086

【Patent Document 8】
JP-A-2000-34266

【Patent Document 9】
JP-A-09-323983

【Patent Document 10】
JP-A-08-311065

【Non-Patent Document 1】
Biochem. Biophys. Res. Commun. 1997, Oct 20; 239 (2)

【Problems to be Solved by the Invention】

Heretofore, non-peptidic low-molecular agonist or antagonist to GPR40 receptor has not been known. Thus, there

is a demand on the development of a superior GRP40 receptor function regulator.

The present invention aims at providing a GPR40 receptor function regulator useful as an insulin secretagogue or agent for the prophylaxis or treatment of diabetes and the like and a novel compound having a GPR40 receptor function regulating action.

【Means of Solving the Problems】

The present inventors have conducted various studies and found that, a carboxylic acid having an aromatic ring and a derivative thereof unexpectedly have a superior GPR40 receptor agonist activity based on a specific chemical structure thereof, and further have superior properties as pharmaceutical products such as stability and the like, and provide safe and useful pharmaceutical agents as agents for the prophylaxis or treatment of GPR40 receptor-related pathology or diseases in mammal, based on which findings completed the present invention.

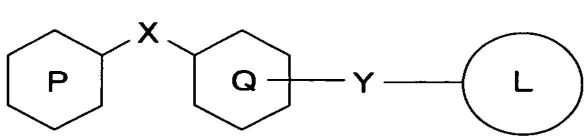
Accordingly, the present invention provides

[1] a GPR40 receptor function regulator comprising a compound having an aromatic ring and a group capable of releasing cation,

[2] the regulator of the above-mentioned [1], which comprises a carboxylic acid having an aromatic ring, or a derivative thereof,

[3] the regulator of the above-mentioned [1], which comprises a carboxylic acid having two or more aromatic rings, or a derivative thereof,

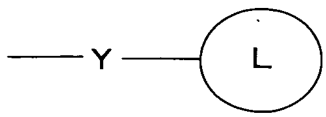
[4] the regulator of the above-mentioned [1], which comprises a compound represented by the formula



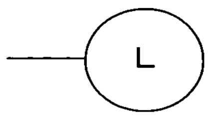
(I')

wherein ring P is an aromatic ring optionally having

substituent(s), ring Q is an aromatic ring optionally further having substituent(s) besides

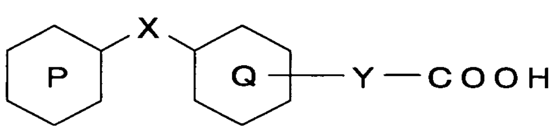
,

X and Y are each a spacer, and



is a group capable of releasing cation, or a salt thereof or a prodrug thereof,

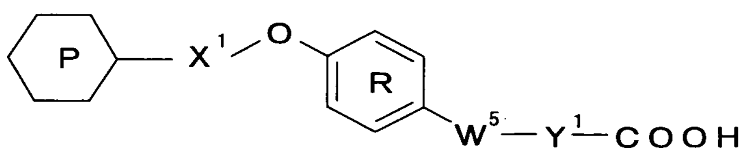
[5] the regulator of the above-mentioned [2], which comprises a compound represented by the formula



(I)

wherein ring P is an aromatic ring optionally having substituent(s), ring Q is an aromatic ring optionally further having substituent(s) besides -Y-COOH, X and Y are each a spacer, and -Y-COOH is substituted at any position on ring Q, or a salt thereof or a prodrug thereof,

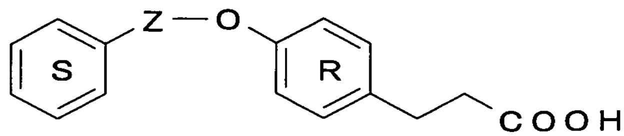
[6] the regulator of the above-mentioned [2], which comprises a compound represented by the formula



(Ia)

wherein ring P is an aromatic ring optionally having substituent(s), ring R is a phenylene group optionally having substituent(s), X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, -O-, -N(R^6)-, -CO-N(R^7)- or -S-, R^6 and R^7 are each a C_{1-6} alkyl group, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s), or a salt thereof or a prodrug thereof,

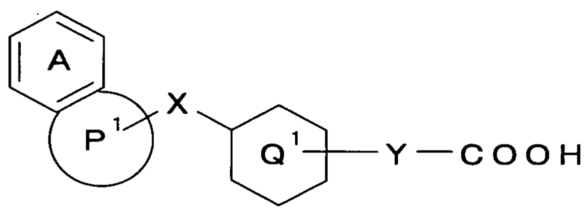
[7] the regulator of the above-mentioned [2], which comprises a compound represented by the formula



(I b)

wherein ring S is a benzene ring optionally having substituent(s), ring R is a phenylene group optionally having substituent(s), and Z is a chain formed by 4 linkages, or a salt thereof or a prodrug thereof,

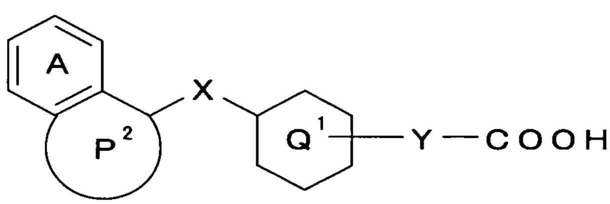
[8] the regulator of the above-mentioned [2], which comprises a compound represented by the formula



(II)

wherein ring A is a benzene ring optionally having substituent(s), ring P^1 is a ring optionally having substituent(s), ring Q^1 is an aromatic ring optionally further having substituent(s) besides -Y-COOH, X and Y are each a spacer, and -Y-COOH is substituted at any potition on ring Q^1, or a salt thereof or a prodrug thereof,

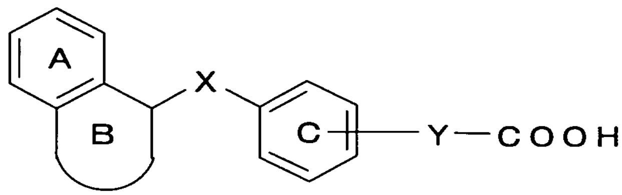
[9] the regulator of the above-mentioned [8], which comprises a compound represented by the formula



(IIa)

wherein ring P^2 is a ring optionally having substituent(s), and other symbols are as defined in the above-mentioned [6], or a salt thereof or a prodrug thereof,

[10] the regulator of the above-mentioned [8], which comprises a compound represented by the formula

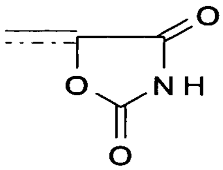
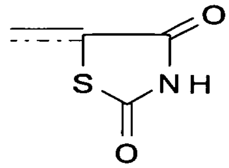
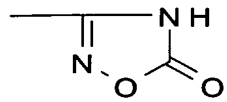
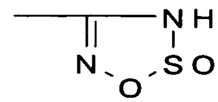


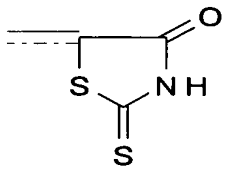
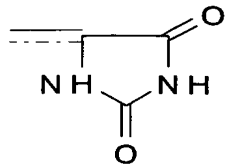
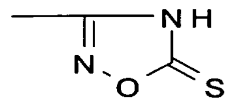
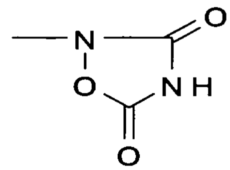
(IIb)

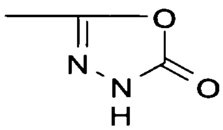
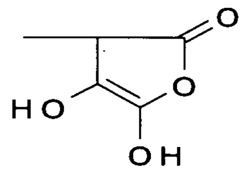
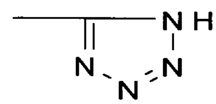
wherein ring A is a benzene ring optionally having substituent(s), ring B is a 5- to 7-membered ring optionally having substituent(s), ring C is a benzene ring optionally further having substituent(s) besides a -Y-COOH group, X and Y are each a spacer, and -Y-COOH is substituted at any position on ring C, or a salt thereof or a prodrug thereof,

[11] the regulator of the above-mentioned [1], wherein the group capable of releasing cation is (1) a 5-membered heterocyclic group capable of releasing cation, (2) a cyano group, (3) a carboxyl group, (4) a C_{2-7} alkoxycarbonyl group, (5) a C_{7-11} aryloxycarbonyl group, (6) a 5 or 6-membered heterocyclyl-oxycarbonyl group containing, besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, (7) a sulfonic acid group, (8) a sulfamoyl group optionally mono-substituted by a C_{1-4} alkyl group, (9) a phosphonic acid group, (10) di-C_{1-4} alkoxyphosphoryl group, (11) a carbamoyl group optionally mono-substituted by a C_{1-4} alkyl group, (12) a C_{2-7} alkylsulfonylthiocarbamoyl group or (13) a trifluoromethanesulfonic acid amido group ($-NHSO_2CF_3$),

[12] the regulator of the above-mentioned [1], wherein the group capable of releasing cation is

, , , ,

, , , ,

,  or ,

[13] the regulator of any one of the above-mentioned [4] to [6], wherein ring P is a benzene ring optionally having substituent(s) or a non-basic aromatic heterocycle optionally having substituent(s),

[14] the regulator of any one of the above-mentioned [4] to [6], wherein ring P is a benzene ring optionally having substituent(s),

[15] the regulator of any one of the above-mentioned [4] to [6], wherein ring P is a benzene ring optionally having substituent(s) at the meta-position,

[16] the regulator of any one of the above-mentioned [4] to [6], wherein the substituent of ring P is a substituent having an aromatic ring,

[17] the regulator of the above-mentioned [16], wherein the substituent having an aromatic ring is a substituent represented by the formula: R^1-E- (R^1 is an aromatic group optionally having substituent(s), and E is a bond or a spacer),

[18] the regulator of the above-mentioned [17], wherein -E- is a bond, -O-, $-CH_2-O-$, -CO-, -CONH- or $-N(R^2)-CH_2-$ (R^2 is a C_{1-6} alkyl group),

[19] the regulator of the above-mentioned [17], wherein -E- is a bond, -O- or $-CH_2-O-$,

[20] the regulator of the above-mentioned [17], wherein R^1 is (i) a phenyl group optionally having substituent(s) selected from the group consisting of a halogen atom and an optionally halogenated C_{1-6} alkyl or (ii) a 5- to 14-membered heterocyclic group containing, besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, which optionally has substituent(s) selected from an optionally halogenated C_{1-6} alkyl, a C_{6-14} aryl and a C_{6-14} aryl-C_{2-6} alkenyl, and E is a bond or $-(CH_2)m^1-W^1-(CH_2)m^2-$ (m^1 and m^2 are each an integer of 0 to 3, W^1 is -O-, $-N(R^2)-$ or $-CO-N(R^3)-$, and R^2 and R^3 are each a C_{1-6} alkyl group),

[21] the regulator of the above-mentioned [5], wherein ring Q is a benzene ring optionally having substituent(s),

[22] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10], wherein the spacer represented by X is (i) $-X^1-W^2-X^2-$ (X^1 and X^2 are each a bond or a C_{1-6} alkylene group optionally having substituent(s), W^2 is -O-, $-N(R^4)-$, $-CO-N(R^5)-$ or -S-, and R^4 and R^5 are each a C_{1-6} alkyl group), or (ii) $-W^3-X^3-W^4-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), W^3 and W^4 are each -O-, $-N(R^4)-$, $-CO-N(R^5)-$ or -S-, and R^4 and R^5 are each a C_{1-6} alkyl group),

[23] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10], wherein the spacer represented by X is $-X^1-O-X^2-$ (X^1 and X^2 are each a bond or a C_{1-6} alkylene group optionally having substituent(s)),

[24] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10], wherein the spacer represented by X is $-X^1-O-$ (X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s)),

[25] the regulator of the above-mentioned [24], wherein X^1 is (i) a bond or (ii) a C_{1-6} alkylene group optionally having substituent(s) selected from a C_{1-6} alkyl and a C_{6-14} aryl,

[26] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10], wherein the spacer represented by X is

(i) a bond,

(ii) $-X^1-O-$ (X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s)),

(iii) $-N(R^4)-X^3-O-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), and R^4 is a C_{1-6} alkyl group),

(iv) $-S-X^3-O-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)),

(v) $-N(R^4)-X^3-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), and R^4 is a C_{1-6} alkyl group),

(vi) $-CO-N(R^5)-$ (R^5 is a C_{1-6} alkyl group),

(vii) $-X^3-S-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)), or

(viii) $-S-X^3-S-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)),

[27] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10], wherein Y is $-W^5-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, -O-, -N(R^6)-, -CO-N(R^7)- or -S-, and R^6 and R^7 are each a C_{1-6} alkyl group),

[28] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10],wherein Y is a C_{1-6} alkylene group optionally having substituent(s),

[29] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10],wherein Y is an ethylene group optionally having substituent(s),

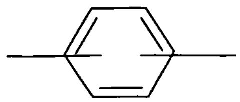
[30] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10],wherein Y is $-O-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)),

[31] the regulator of any one of the above-mentioned [4], [5], [8], [9] and [10],wherein -Y-COOH is substituted at para-position on ring Q, ring Q' or ring C,

[32] the regulator of the above-mentioned [7], wherein Z is (1) a chain formed by 4 linkages selected from $-C(R^8)(R^{8'})-$, -O-, -CO-, $-N(R^{8''})-$ (R^8, $R^{8'}$ and $R^{8''}$ are each a C_{1-6} alkyl group)

and -S-, or

(2) a chain formed by



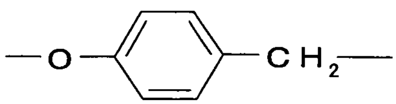
and 2 linkages selected from $-C(R^8)(R^{8'})-$, -O-, -CO-, $-N(R^{8''})-$ (R^8, $R^{8'}$ and $R^{8''}$ are each a C_{1-6} alkyl group) and -S-,

[33] the regulator of the above-mentioned [7], wherein Z is

(1) $-(CH_2)_4-$,

(2) $-O-(CH_2)_3-$,

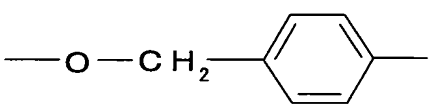
(3)



,

or

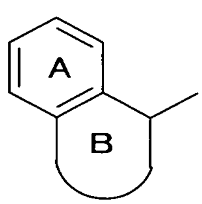
(4)



,

[34] the regulator of the above-mentioned [10], wherein B ring is a 5- to 7-membered ring optionally containing, besides carbon, a nitrogen atom, an oxygen atom or a sulfur atom, which optionally has substituent(s),

[35] the regulator of the above-mentioned [10], wherein



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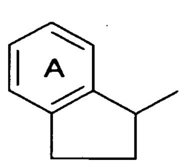

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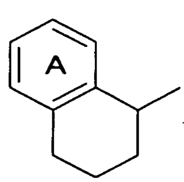

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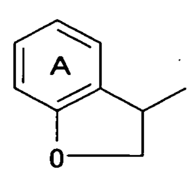
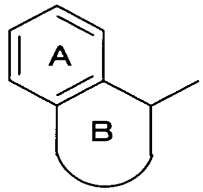


,

[36] the regulator of the above-mentioned [10], wherein



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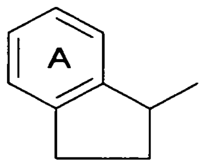

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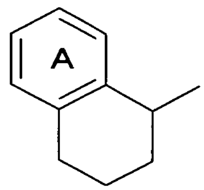


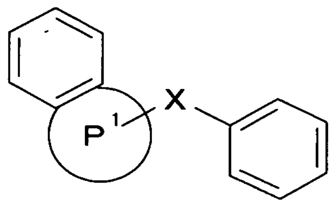
,

[37] the regulator of the above-mentioned [10], wherein the spacer represented by X is a methylene group optionally having substituent(s), -O- or -S-, and the spacer represented by Y is a C_{1-6} alkylene group optionally having substituent(s), $-N(R^6)-Y^1-$ (R^6 is a C_{1-6} alkyl group, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s)), $-O-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)) or $-S-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)),

[38] the regulator of the above-mentioned [1], which is an insulin secretion modulator or a pancreatic β cell protector,

[39] the regulator of the above-mentioned [1], which is an agent for the prophylaxis or treatment of diabetes, impaired glucose tolerance, ketosis, acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hyperlipidemia, genital disorder, skin disease, arthropathy, osteopenia, arteriosclerosis, thrombotic disease, dyspepsia, memory and learning disorder, obesity, hypoglycemia, hypertension, edema, insulin resistance syndrome, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, lipotoxicity or cancer,

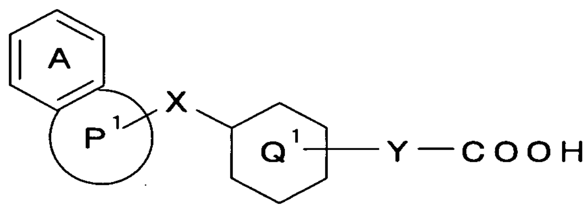
[40] a carboxylic acid having a skeleton represented by the formula



(III)

wherein X is a spacer, and ring P^1 is a ring optionally having substituent(s), or a derivative thereof,

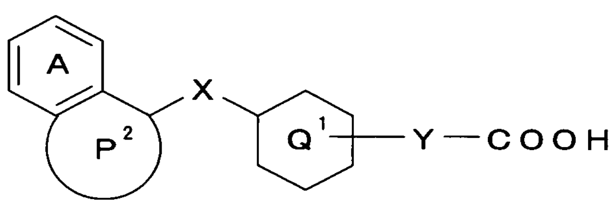
[41] a compound represented by the formula



(II)

wherein ring A is a benzene ring optionally having substituent(s), ring P^1 is a ring optionally having substituent(s), ring Q^1 is an aromatic ring optionally further having substituent(s) besides -Y-COOH, X and Y are each a spacer, and -Y-COOH is substituted at any potition on ring Q^1, or a salt thereof or a prodrug thereof,

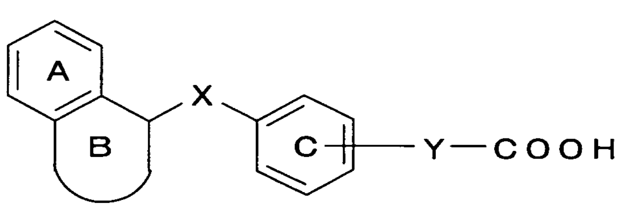
[42] the compound of the above-mentioned [41], which is a compound represented by the formula



(IIa)

wherein ring P^2 is a ring optionally having substituent(s), and other symbols are as defined in the above-mentioned [35], or a salt thereof or a prodrug thereof,

[43] the compound of the above-mentioned [41], which is a compound represented by the formula

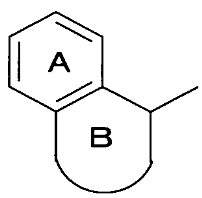


(IIb)

wherein ring A is a benzene ring optionally having substituent(s), ring B is a 5- to 7-membered ring optionally having substituent(s), ring C is a benzene ring optionally further having substituent(s) besides a -Y-COOH group, X and Y are each a spacer, and -Y-COOH is substituted at any position on ring C, or a salt thereof or a prodrug thereof,

[44] the compound of the above-mentioned [43], wherein B ring is a 5- to 7-membered ring optionally containing, besides carbon, a nitrogen atom, an oxygen atom or a sulfur atom, which optionally has substituent(s), or a salt thereof or a prodrug thereof,

[45] the compound of the above-mentioned [43], wherein



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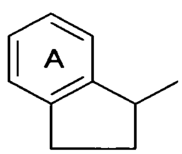
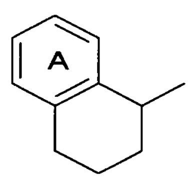
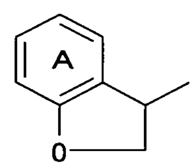
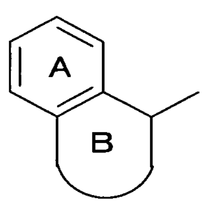
 ,  or  ,

or a salt thereof or a prodrug thereof,

[46] the compound of the above-mentioned [43], wherein



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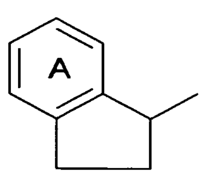
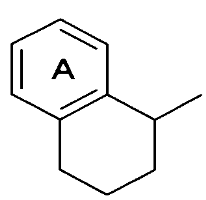
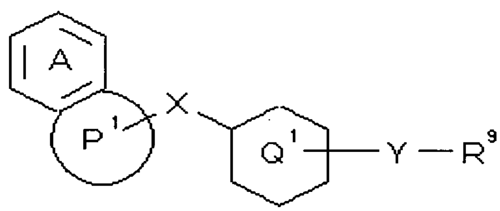
 or  ,

or a salt thereof or a prodrug thereof,

[47] the compound of the above-mentioned [43], wherein the

spacer represented by X is a methylene group optionally having substituent(s), -O- or -S-, and the spacer represented by Y is a C_{1-6} alkylene group optionally having substituent(s), $-N(R^6)-Y^1-$ (R^6 is a C_{1-6} alkyl group, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s)), $-O-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)) or $-S-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)), or a salt thereof or a prodrug thereof,

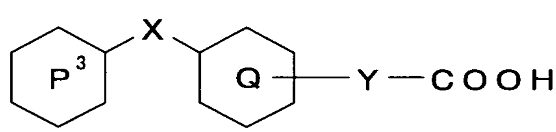
[48] a production method of the compound of the above-mentioned [41] or a salt thereof, wherein comprising subjecting a compound represented by the formula



(IIc)

wherein R^9 is a cyano group or $-COR^{10}$ (R^{10} is an optionally substituted amino group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aryloxy group or an optionally substituted C_{7-16} aralkyloxy group, and the other symbols are defined in the above-mentioned [41], to hydrolysis,

[49] a compound represented by the formula



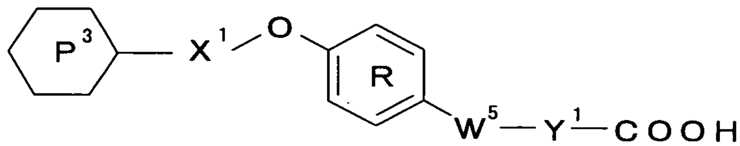
(IV)

wherein ring P^3 is an aromatic ring having substituent(s) having a benzene ring, ring Q is an aromatic ring optionally further having substituent(s) besides -Y-COOH, X and Y are each a spacer, and -Y-COOH is substituted at any position on ring Q, or a salt thereof or a prodrug thereof, except (i) 2-ethoxy-4-[[2-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid, (ii) 2-ethoxy-4-[[3-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid, (iii) 2-ethoxy-4-[[4-[(5-methyl-2-phenyl-4-

oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid, and

(iv) 4-[[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid,

[50] the compound of the above-mentioned [49], which comprises a compound represented by the formula



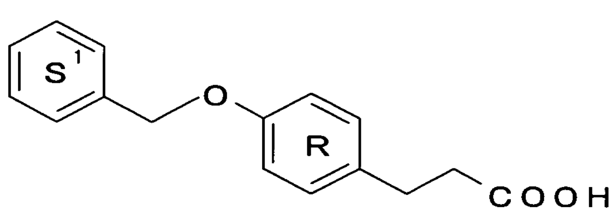
(IVa)

wherein ring P^3 is an aromatic ring having substituent(s) having a benzene ring, ring R is a phenylene group optionally having substituent(s), X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, -O-, -N(R^6)-, -CO-N(R^7)- or -S-, R^6 and R^7 are each a C_{1-6} alkyl group, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s), or a salt thereof or a prodrug thereof,

[51] the compound of the above-mentioned [50], wherein X^1 is a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, and Y^1 is a C_{1-6} alkylene group optionally having substituent(s), or a salt thereof or a prodrug thereof,

[52] the compound of the above-mentioned [50], wherein X^1 is a methylene group optionally having substituent(s), W^5 is a bond, and Y^1 is an ethylene group optionally having substituent(s), or a salt thereof or a prodrug thereof,

[53] the compound of the above-mentioned [49], which is represented by the formula



(IVb)

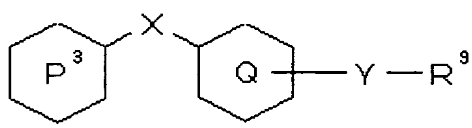
wherein ring S^1 is a benzene ring having substituent(s) having a benzene ring, and ring R is a phenylene group optionally having substituent(s), or a salt thereof or a prodrug thereof,

[54] the compound of any one of the above-mentioned [49] to [53], wherein the substituent(s) having a benzene ring is a substituent represented by the formula: R^{11}-E- (R^{11} is a phenyl group optionally having substituent(s), and E is a bond or a spacer), or a salt thereof or a prodrug thereof,

[55] the compound of the above-mentioned [54], wherein -E- is a bond, -O- or $-CH_2-O-$, or a salt thereof or a prodrug thereof,

[56] the compound of the above-mentioned [54], wherein R^{11} is a phenyl group optionally having substituent(s) selected from the group consisting of a halogen atom and an optionally halogenated C_{1-6} alkyl, or a salt thereof or a prodrug thereof,

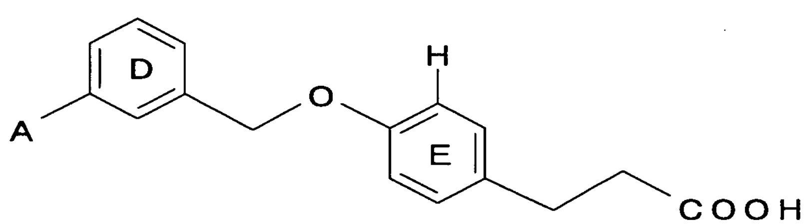
[57] a production method of the compound of the above-mentioned [49] or a salt thereof, wherein comprising subjecting a compound represented by the formula



(IVc)

wherein R^9 is a cyano group or $-COR^{10}$ (R^{10} is an optionally substituted amino group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aryloxy group or an optionally substituted C_{7-16} aralkyloxy group, and the other symbols are defined in the above-mentioned [49], to hydrolysis,

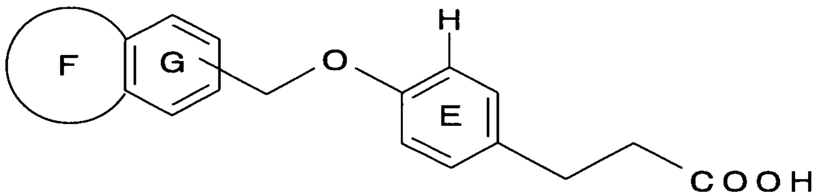
[58] a compound represented by the formula



(A)

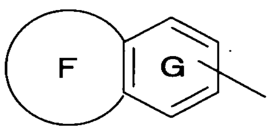
wherein A is a substituent (except a hydrogen atom and a chlorine atom), ring D is a benzene ring optionally further having, besides A, substituent(s) (except a nitro group and a hydroxy group), and ring E is a phenylene group optionally having substituent(s), or a salt thereof or a prodrug thereof, except 2-ethoxy-4-[[3-[(5-methyl-2-phenyl-4-

oxazolyl)methoxy]phenyl]methoxy]benzenepropanoic acid, [59] the compound of the above-mentioned [58], wherein A is a bromine atom, or a salt thereof or a prodrug thereof, [60] a compound represented by the formula

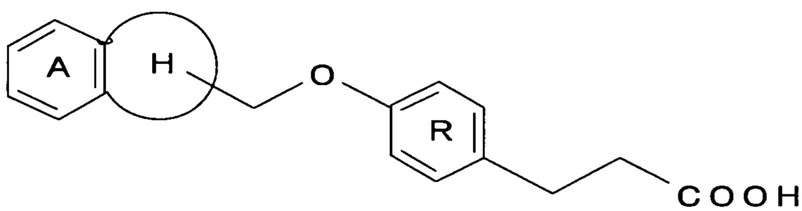


(B)

wherein ring F is a ring optionally having substituent(s), ring G is a benzene ring optionally having substituent(s), and ring E is a phenylene group optionally having substituent(s), provided that

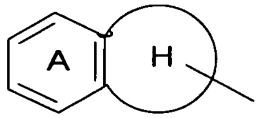


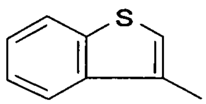
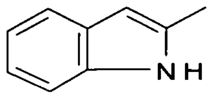
is not an unsubstituted naphthyl group, an unsubstituted 1H-indazolyl group and a quinolyl group optionally having substituent(s), or a salt thereof or a prodrug thereof, [61] a compound represented by the formula



(C)

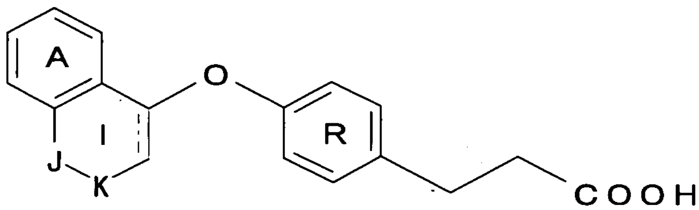
wherein ring A is a benzene ring optionally having substituent(s), ring H is a 5-membered ring optionally having substituent(s), and ring R is a phenylene group optionally having substituent(s), or a salt thereof or a prodrug thereof, except 3,5-dibromo-4-[(5-chlorobenzo[b]thiophen-3-yl)methoxy]benzenepropanoic acid, 4-(1H-benzotriazol-1-ylmethoxy)benzenepropanoic acid and 4-(1H-indol-3-ylmethoxy)benzenepropanoic acid, [62] the compound of the above-mentioned [61], wherein

 is

 or  ,

or a salt thereof or a prodrug thereof,

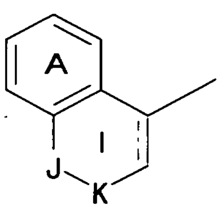
[63] a compound represented by the formula

 (D)

wherein ring A is a benzene ring optionally having substituent(s), J is -O-, -S-, $-CH_2-$ or $-NR^{12}-$ (R^{12} is a C_{1-6} alkyl group), K is a bond or a C_{1-3} alkylene group,

is a single bond or a double bond, ring R is a phenylene group optionally having substituent(s), and ring I optionally has substituent(s), or a salt thereof or a prodrug thereof,

[64] the compound of the above-mentioned [63], wherein



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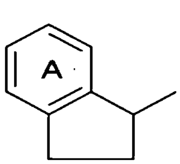
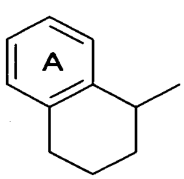
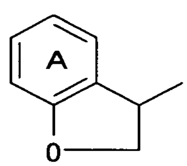
 ,  or  ,

the substituent of ring A is (i) a halogen atom, (ii) a C_{1-6} alkyl group, (iii) a C_{1-6} alkoxy group, (iv) a C_{6-14} aryl group optionally having substituent(s) selected from a halogen atom

and a C_{1-6} alkyl, (v) a C_{6-14} aryloxy group or (vi) a C_{7-15} aralkyloxy group, and the substituent of ring R is a halogen atom, or a salt thereof or a prodrug thereof,

[65] a pharamaceutical composition comprising the compound of any one of the above-mentioned [40], [41], [49], [58], [60], [61] and [63] or a salt thereof or a prodrug thereof,

[66] the pharamaceutical composition of the above-mentioned [65], which is a GPR40 receptor function regulator,

[67] the pharamaceutical composition of the above-mentioned [65], which is An insulin secretion modulator or a pancreatic β cell protector,

[68] the pharamaceutical composition of the above-mentioned [65], which is an agent for the prophylaxis or treatment of diabetes, impaired glucose tolerance, ketosis, acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hyperlipidemia, genital disorder, skin disease, arthropathy, osteopenia, arteriosclerosis, thrombotic disease, dyspepsia, memory and learning disorder, obesity, hypoglycemia, hypertension, edema, insulin resistance syndrome, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, lipotoxicity or cancer,

[69] a method of regulating a GPR40 receptor function, which comprises administering an effective amount of a carboxylic acid having an aromatic ring or a derivative thereof to a mammal, and

[70] Use of a carboxylic acid having an aromatic ring or a derivative thereof for the production of a GPR40 receptor function regulator.

The compound to be used in the present invention is a compound having an aromatic ring and a group capable of releasing cation, which is preferably a carboxylic acid having an aromatic ring or a derivative thereof, more preferably a carboxylic acid having 2 or more aromatic rings or a

derivative thereof, specifically, the above-mentioned compound (I′), compound (I), compound (Ia), compound (Ib), compound (II), compound (IIa), compound (IIb), compound (IIc), compound (III), compound (IV), compound (IVa), compound (IVb), compound (IVc), compound (A), compound (B), compound (C) and compound (D).

In the present specification, the aromatic ring means an aromatic hydrocarbon ring or an aromatic heterocycle.

As the aromatic hydrocarbon ring, a hydrocarbon ring having 6 to 14 carbon atoms, such as a benzene ring, a naphthalene ring and the like, can be used, with preference given to a benzene ring.

As the aromatic heterocycle, for example, a 5- to 14-membered (monocyclic, bicyclic or tricyclic), preferably 5- to 10-membered, more preferably 5- or 6-membered aromatic heterocycle containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom can be used. As the above-mentioned "5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle", for example, aromatic heterocycles such as thiophene, furan, oxazole, benzo[b]thiophene, benzo[b]furan, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, isoxazole, furazan, phenoxazine and the like, rings formed by condensation of these rings (preferably monocycle) with one or plural (preferably 1 or 2) aromatic rings (e.g., benzene ring etc.) and the like can be used. Of these, a non-basic aromatic heterocycle is preferable, for example, aromatic

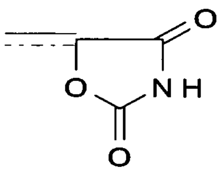
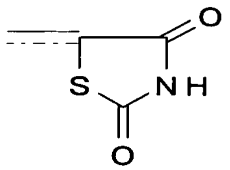
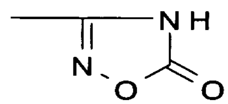
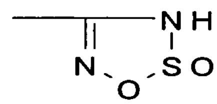
heterocycles such as thiophene, benzo[b]thiophene, benzo[b]furan, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, indole, carbazole, thiazole, isothiazole, isoxazole and the like, rings formed by condensation of these rings (preferably monocycle) with one or plural (preferably 1 or 2) non-basic aromatic rings (e.g., benzene ring etc.) and the like can be used.

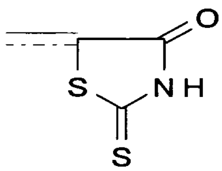
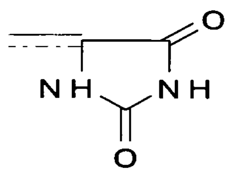
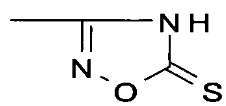
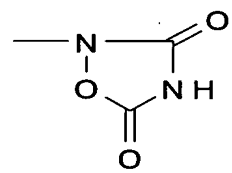
In the present specification, the group capable of releasing cation may be a group capable of releasing cation chemically (e.g., by chemical reactions such as oxidation, reduction, hydrolysis and the like, and the like) or biologically, namely under physiological conditions (e.g., in vivo reactions such as oxidation, reduction, hydrolysis and the like due to biological enzymes, and the like), or a group capable of converting to such group.

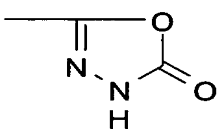
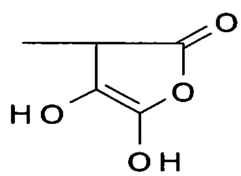
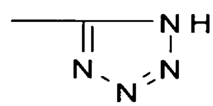
As the group capable of releasing cation, for example, (1) a 5-membered heterocyclic group capable of releasing cation, (2) a cyano group, (3) a carboxyl group, (4) a C_{2-7} alkoxycarbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl and the like), (5) a C_{7-11} aryloxycarbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl and the like), (6) a 5 or 6-membered heterocyclyl-oxycarbonyl group containing, besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom (e.g., pyridyloxycarbonyl, thienyloxycarbonyl and the like), (7) a sulfonic acid group, (8) a sulfamoyl group optionally mono-substituted by a C_{1-4} alkyl group (e.g., methyl, ethyl, propyl, butyl, isobutyl, tert-butyl and the like), (9) a phosphonic acid group, (10) di-C_{1-4} alkoxyphosphoryl group (e.g., dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl and the like), (11) a carbamoyl group optionally mono-substituted by a C_{1-4} alkyl group (e.g., methyl, ethyl, propyl, butyl, isobutyl, tert-butyl and the like), (12) a C_{2-7} alkylsulfonylthiocarbamoyl group (e.g.,

methylsulfonylthiocarbamoyl, ethylsulfonylthiocarbamoyl etc.), (13) a trifluoromethanesulfonic acid amido group ($-NHSO_2CF_3$) and the like can be used.

As the above-mentioned 5-membered heterocyclic group capable of releasing cation, a 5-membered heterocyclic group comprising 1 to 4 selected from N, O and S as ring-constituting atom(s) and the like can be used. For example,

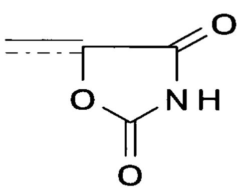
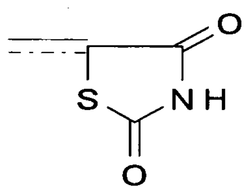
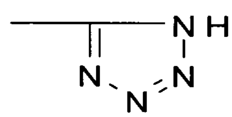
 ,  ,  ,  ,

 ,  ,  ,  ,

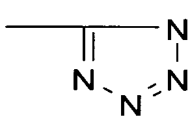
 ,   .

and the like can be mentioned.

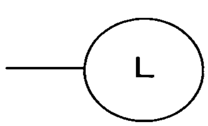
The group capable of releasing cation is preferably 5-membered heterocyclic group, more preferably

 ,  or  ,

particularly preferably

 ,

which is capable of releasing cation.



is a group capable of releasing cation.

Ring P is an aromatic ring optionally having substituent(s).

As the aromatic ring represented by ring P, a benzene ring, and non-basic aromatic heterocycles such as thiophene, benzo[b]thiophene, benzo[b]furan, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, indole, carbazole, thiazole, isothiazole, isoxazole and the like are preferable, and a benzene ring is particularly preferable.

Ring Q is an aromatic ring optionally further having substituent(s) besides -Y-COOH.

As the aromatic ring represented by ring Q, a benzene ring, and non-basic aromatic heterocycles such as thiophene, benzo[b]thiophene, benzo[b]furan, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, indole, carbazole, thiazole, isothiazole, isoxazole and the like are preferable, and a benzene ring is particularly preferable.

As the aforementioned substituent that the ring P may have, and as the aforementioned substituent that the ring Q may further have besides -Y-COOH, for example, a substituent selected from a substituent selected from a oxo; a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.); a C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy etc.); a nitro; a cyano; an optionally substituted lower(C_{1-6}) alkyl; an optionally substituted lower(C_{2-6}) alkenyl; an optionally substituted lower(C_{2-6}) alkynyl; an optionally substituted C_{3-8} cycloalkyl; an optionally substituted C_{6-14} aryl; an optionally substituted C_{7-16} aralkyl; an optionally substituted lower(C_{1-6}) alkoxy; a hydroxy; an optionally substituted C_{6-14} aryloxy; an optionally substitute C_{7-16} aralkyloxy; a mercapto; an optionally substituted lower(C_{1-6}) alkylthio; an optionally substituted C_{6-14} arylthio; an optionally substitute C_{7-16} aralkylthio; an optionally substituted amino; a formyl; a carboxy; an optionally substituted lower(C_{1-6}) alkyl-carbonyl

(e.g., acetyl, propionyl, pivaloyl etc.); an optionally substituted C_{3-8} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclpentylcarbonyl, cyclohexylcarbonyl, 1-methyl-cyclohexyl-carbonyl etc.); a C_{6-14} aryl-carbonyl (e.g., benzoly, 1-naphtoyl, 2-naphtoyl etc.); a C_{7-16} aralkyl-carbonyl (e.g., phenylacetyl, 3—naphtoylpropionyl etc.); an optionally substituted 5 to 7-menbered heterocyclylcarbonyl containing, besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom (e.g., nicotinoyl, isonicotinoyl, thenoyl, furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl etc.); an optionally esterified carboxy; an optionally substituted carbamoyl; a lower(C_{1-6}) alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl etc.); a lower(C_{1-6}) alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl etc.); a C_{6-14} arylsulfonyl(e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl etc.); a C_{6-14} arylsulfinyl (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl etc.); a formylamino; an optionally substituted lower(C_{1-6}) alkyl-carbonylamino (e.g., acetylamino, propionylamino, pivaloylamino etc.); an optionally substituted C_{3-8} cycloalkyl-carbonylamino (e.g., cyclopropylcarbonylamino, cyclpentylcarbonylamino, cyclohexylcarbonylamino etc.); an optionally substituted C_{6-14} aryl-carbonylamino (e.g., benzoylamino, naphtoylamino etc.); an optionally substituted lower(C_{1-6}) alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino etc.); an optionally substituted lower(C_{1-6}) alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino etc.); a C_{6-14} arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino etc.); an optionally substituted lower(C_{1-6}) alkyl-carbonyloxy (e.g., acetoxy, propionyloxy etc.); an optionally substituted C_{6-14} aryl-carbonyloxy (e.g., benzoyloxy, naphthylcarbonyloxy etc.); an optionally substituted lower(C_{1-6}) alkoxy-carbonyloxy (e.g.,

methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy etc.); an optionally substituted mono-lower(C_{1-6}) alkyl-carbamoyloxy (e.g., methylcarbamoyloxy, ethylcarbamoyloxy etc.); an optionally substituted di-lower(C_{1-6}) alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy etc.); an optionally substituted mono- or di-C_{6-14} aryl-carbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy etc.); an optionally substituted heterocyclic group; a sulfo; a sulfamoyl; a sulfinamoyl; a sulfenamoyl; a group wherein two or more (e.g., 2-3) of these substituents are bonded; and the like (hereinafter to be abbreviated as substituent group A) can be used. Ring P may have 1 to 5, preferably 1 to 3, substituents mentioned above at substitutable position(s), and when the number of the substituents is not less than 2, respective substituents may be the same or different.

As the "optionally esterified carboxyl group" in the substituent group A, for example, a C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl etc.), a C_{6-14} aryloxy-carbonyl (e.g., phenoxycarbonyl etc.), a C_{7-16} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl etc.) and the like can be used.

As the "lower(C_{1-6}) alkyl" of the "optionally substituted lower(C_{1-6}) alkyl" in the substituent group A, for example, methyl, chloromethyl,ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl and the like can be used.

As the "lower(C_{2-6}) alkenyl" of the "optionally substituted lower(C_{2-6}) alkenyl" in the substituent group A, for example, vinyl, propenyl, isopropenyl, 2-buten-1-yl, 4-penten-1-yl, 5-hexen-1-yl and the like can be used.

As the "lower(C_{2-6}) alkynyl" of the "optionally substituted lower(C_{2-6}) alkynyl" in the substituent group A,

for example, 2-butyn-1-yl, 4-pentyn-1-yl, 5-hexyn-1-yl and the like can be used.

As the "C_{3-8} cycloalkyl" of the "optionally substituted C_{3-8} cycloalkyl" in the substituent group A, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like can be used.

As the "C_{6-14} aryl" of the "optionally substituted C_{6-14} aryl" in the substituent group A, for example, phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl and the like can be used.

As the "C_{7-16} aralkyl" of the "optionally substituted C_{7-16} aralkyl" in the substituent group A, for example, benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 2-biphenylylmethyl, 3-biphenylylmethyl, 4-biphenylylmethyl) and the like can be used.

As the "lower(C_{1-6}) alkoxy" of the "optionally substituted lower(C_{1-6}) alkoxy" in the substituent group A, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy and the like can be used.

As the "C_{6-14} aryloxy" of the "optionally substituted C_{6-14} aryloxy" in the substituent group A, for example, phenyloxy, 1-naphthyloxy, 2-naphthyloxy and the like can be used.

As the "C_{7-16} aralkyloxy" of the "optionally substituted C_{7-16} aralkyloxy" in the substituent group A, for example, benzyloxy, phenethyloxy and the like can be used.

As the "lower(C_{1-6}) alkylthio" of the "optionally substituted lower(C_{1-6}) alkylthio" in the substituent group A, for example, methylthio, ethylthio, propylthio, isopropylthio, propylthio, sec-propylthio, tert-propylthio and the like can be used.

As the "C_{6-14} arylthio" of the "optionally substituted C_{6-14} arylthio" in the substituent group A, for example, phenylthio, 1-naphthylthio, 2-naphthylthio and the like can be used.

As the "C_{7-16} aralkylthio" of the "optionally substituted C_{7-16} aralkylthio" in the substituent group A, for example, benzylthio, phenethylthio and the like can be used.

These "lower alkyl group", "lower alkenyl", "lower alkynyl", " C_{3-8} cycloalkyl", "lower alkoxy", "C_{6-14} aryloxy", "C_{7-16} aralkyloxy", "lower alkylthio", "C_{6-14} arylthio" and "C_{7-16} aralkylthio" each optionally have 1 to 5 substituents selected from, for example, a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom, iodine atom); carboxyl; hydroxy; amino; mono- or di-lower(C_{1-6}) alkylamino; mono- or di-C_{6-14} arylamino; C_{3-8} cycloalkyl; optionally halogenated lower(C_{1-6}) alkoxy; lower(C_{1-6}) alkoxy-carbonyl; lower(C_{1-6}) alkylthio; lower(C_{1-6}) alkylsulfinyl; lower(C_{1-6}) alkylsulfonyl; the above-mentioned optionally esterified carboxyl; carbamoyl; thiocarbamoyl; mono-lower(C_{1-6}) alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl etc.); di-lower(C_{1-6}) alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl etc.); mono- or di-C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl etc.); mono- or di- 5- to 7-membered heterocyclylcarbamoyl containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl etc.) and the like.

The "C_{6-14} aryl" and "C_{7-16} aralkyl" in the substituent group A each may have 1 to 5 substituents selected from, for example, a halogen atom; hydroxy; carboxyl; nitro; cyano; the above-mentioned optionally substituted lower alkyl; the above-mentioned optionally substituted lower alkenyl; the above-mentioned optionally substituted lower alkynyl; the above-mentioned optionally substituted C_{3-8} cycloalkyl; the above-mentioned optionally substituted lower alkoxy; the above-mentioned optionally substituted lower alkylthio; the above-

mentioned optionally substituted lower alkylsulfinyl; the above-mentioned optionally substituted lower alkylsulfonyl; the above-mentioned optionally esterified carboxyl; carbamoyl; thiocarbamoyl; mono-lower(C_{1-6}) alkyl-carbamoyl; di-lower(C_{1-6}) alkyl-carbamoyl; mono- or di-C_{6-14} aryl-carbamoyl; mono- or di-5- to 7-membered heterocyclylcarbamoyl containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom; and the like.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" in the substituent group A, for example, a 5- to 14-membered (monocycle, bicyclic or tricyclic) heterocyclic group containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, preferably (i) 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group, (ii) a 5- to 10-membered non-aromatic heterocyclic group, (iii) a monovalent group obtained by removing any one hydrogen atom from a 7- to 10-membered crosslinked heterocycle, and the like can be used, with preference given to a 5-membered aromatic heterocyclic group. Specifically, for example, aromatic heterocyclic groups such as thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-

isoxazolyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, benzo[b]thienyl (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl), benzo[b]furanyl (e.g., 2-benzo[b]furanyl, 3-benzo[b]furanyl) and the like; non-aromatic heterocyclic groups such as pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), oxazolidinyl (e.g., 2-oxazolidinyl), imidazolinyl (e.g., 1-imidazolinyl, 2-imidazolinyl, 4-imidazolinyl), piperidinyl (e.g., 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl), morpholino, thiomorpholino and the like; and the like can be used.

The heterocyclic group may have 1 to 5 substituents selected from, for example, a halogen atom; hydroxy; carboxyl; nitro; cyano; the above-mentioned optionally substituted lower alkyl; the above-mentioned optionally substituted lower alkenyl; the above-mentioned optionally substituted lower alkynyl; the above-mentioned optionally substituted C_{3-8} cycloalkyl; the above-mentioned optionally substituted C_{6-14} aryl; the above-mentioned optionally substituted lower alkoxy; the above-mentioned optionally substituted lower alkylthio; the above-mentioned optionally substituted C_{6-14} arylthio; the above-mentioned optionally substituted C_{7-16} aralkylthio; the above-mentioned optionally substituted lower alkylsulfinyl; the above-mentioned optionally substituted C_{6-14} arylsulfinyl; the above-mentioned optionally substituted C_{1-6} alkylsulfonyl; the above-mentioned optionally substituted C_{6-14} arylsulfonyl; the above-mentioned optionally esterified carboxyl; carbamoyl; thiocarbamoyl; mono-lower(C_{1-6}) alkyl-carbamoyl; di-lower(C_{1-6}) alkyl-carbamoyl; mono- or di-C_{6-14} aryl-carbamoyl; mono- or di-5- to 7-membered heterocyclylcarbamoyl containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom; and the like.

As the "optionally substituted carbamoyl group" in the

substituent group A, a carbamoyl group optionally substituted by the above-mentioned optionally substituted lower alkyl, the above-mentioned optionally substituted lower alkenyl, the above-mentioned optionally substituted lower alkynyl, the above-mentioned optionally substituted C_{3-8} cycloalkyl, the above-mentioned optionally substituted C_{6-14} aryl, the above-mentioned optionally substituted heterocyclic group and the like can be used, and specifically, for example, carbamoyl; thiocarbamoyl; mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl etc.); di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl etc.); C_{1-6} alkyl(C_{1-6} alkoxy)-carbamoyl (e.g., methyl(methoxy)carbamoyl, ethyl(methoxy)carbamoyl); mono- or di-C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl etc.); mono- or di- 5- to 7-membered heterocyclylcarbamoyl containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl etc.); 5 to 7-membered cyclylcarbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, hexamethyleneiminocarbonyl) and the like can be used.

As the "optionally substituted amino" in the substituent group A, an amino optionally substituted by 1 or 2 substituent(s) selected from the above-mentioned optionally substituted lower alkyl, the above-mentioned optionally substituted lower alkenyl, the above-mentioned optionally substituted lower alkynyl, the above-mentioned optionally substituted C_{3-8} cycloalkyl, the above-mentioned optionally substituted C_{6-14} aryl, the above-mentioned optionally substituted lower alkoxy and the like can be used.

As the substituent of ring P, a substituent having an

aromatic ring is preferable. Specifically, a substituent represented by the formula: R^1-E- (R^1 is an aromatic group optionally having substituent(s), and E is a bond or a spacer) and the like can be used.

As the "aromatic group" of the "aromatic group optionally having substituent(s)" represented by R^1, an aromatic hydrocarbon group and an aromatic heterocyclic group can be used.

As the aromatic hydrocarbon group, a C_{6-14} aryl group such as a phenyl group, a naphthyl group and the like can be used, with preference given to a phenyl group.

As the aromatic heterocyclic group, for example, a 5- to 14-membered (monocycle, bicyclic or tricyclic) aromatic heterocyclic group containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, preferably (i) a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group, (ii) a monovalent group obtained by removing any one hydrogen atom from a 7- to 10-membered aromatic crosslinked heterocycle, and the like can be mentioned, with preference given to a monocyclic aromatic heterocyclic group. Specifically, for example, thienyl (e.g., 2-thienyl, 3-thienyl), furyl (e.g., 2-furyl, 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl), pyrazinyl, pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), isothiazolyl (e.g., 3-isothiazolyl), isoxazolyl (e.g., 3-isoxazolyl), indolyl (e.g.,

1-indolyl, 2-indolyl, 3-indolyl), 2-benzothiazolyl, benzo[b]thienyl (e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl), benzo[b]furanyl (e.g., 2-benzo[b]furanyl, 3-benzo[b]furanyl) and the like can be used.

As the "substituent" of the "aromatic group" represented by R^1, a substituent selected from the aforementioned substituent group A can be used.

As R^1, (i) a phenyl group optionally having substituent(s) selected from the group consisting of a halogen atom and an optionally halogenated C_{1-6} alkyl, or (ii) a 5- to 14-membered aromatic heterocyclic group containing, besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom (e.g., thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl) and the like), which optionally has substituent(s) selected from optionally a C_{1-6} alkyl, a C_{6-14} aryl and a C_{6-14} aryl-C_{2-6} alkenyl, is preferable.

As the spacer represented by E, an alkylene group optionally having substituent(s) wherein -C- in the alkylene group is optionally substituted by -O-, -N- or -S-, can be used. The position at which -C- in the alkylene group is substituted by -O-, -N- or -S- may be the terminal or chain of the alkylene group.

As the "alkylene group" of the "alkylene group optionally having substituent(s)" for the spacer represented by E, for example, a C_{1-13} alkylene group (e.g., methylene, ethylene, propylene, butylene and the like) can be used, and a C_{1-6} alkylene group is particularly preferable.

As the substituent of the "alkylene group", a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl) and the like can be preferably used.

Specifically, as E,

(i) a bond, or

(ii) a spacer represented by $-(CH_2)m^1-W^1-(CH_2)m^2-$ (m^1 and m^2 are each an integer of 0 to 3, W^1 is -O-, $-N(R^2)-$ or $-CO-N(R^3)-$, and R^2 and R^3 are each or a C_{1-6} alkyl group) is preferable.

As m^1, 0 or 1 is preferable.

As m^2, 0 or 1 is preferable.

As a combination of m^1 and m^2, the both being 0, or one being 0 and the other being 1 is preferable.

As the C_{1-6} alkyl group represented by R^2 or R^3, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl can be used.

Particularly, as E, a bond, -O-, $-CH_2-O-$, -CO-, -CONH- or $-N(R^2)-CH_2-$ (R^2 is a C_{1-6} alkyl group) is preferable, particularly, a bond, -O- or $-CH_2-O-$ is preferable.

When ring P is a benzene ring, a compound wherein ring P has a substituent at the meta-position, is preferable.

X and Y are each a spacer, and as the spacer, "an alkylene group optionally having substituent(s), wherein -C- in the alkylene group is optionally substituted by -O-, -N- or -S-" can be used, like the aforementioned spacer represented by E.

As the spacer represented by X,

(i) $-X^1-W^2-X^2-$ (X^1 and X^2 are each a bond or a C_{1-6} alkylene group optionally having substituent(s), W^2 is -O-, $-N(R^4)-$, $-CO-N(R^5)-$ or -S-, and R^4 and R^5 are each a C_{1-6} alkyl group), or

(ii) $-W^3-X^3-W^4-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), W^3 and W^4 are each -O-, $-N(R^4)-$, $-CO-N(R^5)-$ or -S-, and R^4 and R^5 are each a C_{1-6} alkyl group) is preferable.

As the "C_{1-6} alkylene group" of the "C_{1-6} alkylene group optionally having substituent(s)" represented by X^1, X^2 or X^3, methylene, ethylene, propylene, butylene, pentylene and hexylene can be used, and particularly, a C_{1-4} alkylene group such as methylene, ethylene, propylene and butylene is preferable.

As the C_{1-6} alkyl group represented by R^4 or R^5, methyl, chloromethyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl and hexyl can be used.

As W^2, -O- or the like is preferable.

As W^3 and W^4, -S- or the like is preferable.

Particularly, the spacer represented by X, $-X^1-O-X^2-$ (X^1 and X^2 are each a bond or a C_{1-6} alkylene group optionally having substituent(s)) is preferable, and particularly, $-X^1-O-$ (X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s)) is preferable.

As X^1, a bond or a C_{1-6} alkylene group (particularly, a C_{1-4} alkylene group) optionally having substituent(s) selected from a C_{1-6} alkyl and a C_{6-14} aryl is preferable.

As the combination of X^1 and X^2, the both being bonds, or one of them being a bond is preferable.

More specifically, as the spacer represented by X,
(i) a bond,
(ii) $-X^1-O-$ (X^1 is a bond or a C_{1-6} alkylene group optionally having substituent(s)),
(iii) $-N(R^4)-X^3-O-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), and R^4 is a C_{1-6} alkyl group),
(iv) $-S-X^3-O-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)),
(v) $-N(R^4)-X^3-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s), and R^4 is a C_{1-6} alkyl group),
(vi) $-CO-N(R^5)-$ (R^5 is a C_{1-6} alkyl group),
(vii) $-X^3-S-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)), or
(viii) $-S-X^3-S-$ (X^3 is a C_{1-6} alkylene group optionally having substituent(s)) or the like is preferable.

As Y, $-W^5-Y^1-$ (Y^1 is a C_{1-6} alkylene group optionally having substituent(s), W^5 is a bond, -O-, $-N(R^6)-$, $-CO-N(R^7)-$ or -S-, and R^6 and R^7 are each a C_{1-6} alkyl group) or the like

is preferable.

As the "C_{1-6} alkylene group" of the "C_{1-6} alkylene group optionally having substituent(s)" represented by Y^1, methylene, ethylene, propylene, butylene, pentylene and hexylene can be used, and particularly, a C_{1-4} alkylene group such as methylene, ethylene, propylene and butylene is preferable.

As the C_{1-6} alkyl group represented by R^6 or R^7, methyl, chloromethyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl and hexyl can be used.

As W^5, a bond or -O- is preferable, and a bond is particularly preferable.

Particularly, as Y, (i) a C_{1-6} alkylene group optionally having substituent(s) or (ii) -O-Y^1- (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)) is preferable, and particularly, a C_{1-6} alkylene group (e.g., methylene, ethylene, propylene) optionally having substituent(s) is preferable, and an ethylene group optionally having substituent(s) is particularly preferable. In addition, a C_{1-6} alkylene group is preferably unsubstituted.

-Y-COOH may be bonded at any position on ring Q, ring Q^1 or ring C. When ring Q, ring Q^1 or ring C is a benzene ring (phenyl group), these rings are preferably bonded at the para-position.

Ring R is a phenylene group optionally having substituent(s). As the substituent that a phenylene group represented by ring R may have, those similar to the above-mentioned substituent that ring P may have can be used, and particularly, a C_{1-6} alkoxy and the like can be preferably used.

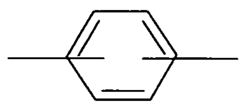
Ring S is a benzene ring optionally having substituent(s). As the substituent that the benzene ring represented by ring S may have, those similar to the above-mentioned substituent that ring P may have can be used.

Z is a chain formed by 4 linkages. As the chain

represented by Z,

(1) a chain formed by 4 linkages selected from -C(R^8)($R^{8'}$)-, -O-, -CO-, -N($R^{8''}$)- (R^8, $R^{8'}$ and $R^{8''}$ are each a C_{1-6} alkyl group) and -S-,

(2) a chain formed by

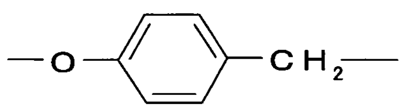


and 2 linkages selected from -C(R^8)($R^{8'}$)-, -O-, -CO-, -N($R^{8''}$)- (R^8, $R^{8'}$ and $R^{8''}$ are each a C_{1-6} alkyl group) and -S-, or the like can be used, and specifically,

(1) -(CH_2)$_4$-,

(2) -O-(CH_2)$_3$-,

(3)



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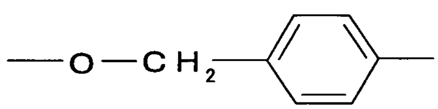
(4)



or the like can be used.

Ring A is a benzene ring optionally having substituent(s). As the substituent that the benzene ring represented by ring A may have, those similar to the above-mentioned substituent that ring P may have can be used.

Ring P^1 and ring P^2 are each a ring optionally having substituent(s).

As the ring represented by ring P^1 or ring P^2, a carbon ring or a heterocycle can be used.

As the carbon ring, (1) a cycloalkane having 5 to 7 carbon atoms such as cyclopentane, cyclohexane and the like, (2) an aromatic hydrocarbon ring having 6 to 14 carbon atoms

such as a benzene ring, a naphthalene ring and the like can be used, and particularly, a cycloalkane having 5 to 7 carbon atoms such as cyclohexane and the like can be preferably used.

As the heterocycle, for example, a 5- to 14-membered (monocycle, bicyclic or tricyclic) heterocycle containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom, preferably (i) a 5- to 14-membered, preferably 5- to 10-membered, more preferably 5- or 6-membered, aromatic heterocycle, (ii) a 5- to 10-membered non-aromatic heterocycle, (iii) a 7- to 10-membered crosslinked heterocycle and the like can be used.

As the above-mentioned "5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle", for example, aromatic heterocycles such as thiophene, furan, oxazole, benzo[b]thiophene, benzo[b]furan, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, isoxazole, furazan, phenoxazine and the like, rings formed by condensation of these rings (preferably monocycle) with one or plural (preferably 1 or 2) aromatic rings (e.g., benzene ring etc.) and the like can be used.

As the above-mentioned "5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle", for example, aromatic heterocycles such as thiophene, benzo[b]thiophene, benzo[b]furan, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-

quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, isoxazole, furazan, phenoxazine and the like, rings formed by condensation of these rings (preferably monocycle) with one or plural (preferably 1 or 2) aromatic rings (e.g., benzene ring etc.) and the like can be used.

As the above-mentioned "5- to 10-membered non-aromatic heterocycle", for example, pyrrolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine, dioxazole, oxadiazoline, thiadiazoline, triazoline, thiadiazole, dithiazole and the like can be mentioned.

As the above-mentioned "7- to 10-membered crosslinked heterocycle", for example, quinuclidine, 7-azabicyclo[2.2.1]heptane and the like can be mentioned.

As ring P^1 and ring P^2, a carbon ring is preferable, and particularly, a cycloalkane having 5 to 7 carbon atoms such as cyclohexane or the like is preferable.

As the substituent that a ring represented by ring P^1 or ring P^2 may have, those similar to the above-mentioned substituent that ring P may have can be used.

Ring Q^1 is an aromatic ring optionally further having substituent(s) besides -Y-COOH.

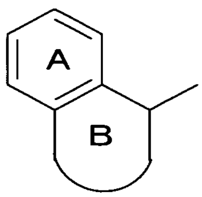
As the aromatic ring represented by ring Q^1, those similar to the aforementioned aromatic ring represented by ring Q can be used, and particularly, an aromatic hydrocarbom such as a benzene ring is preferable.

As the substituent that the ring represented by ring Q^1 may have besides -Y-COOH, those similar to the above-mentioned substituent that ring P may have can be used.

Ring B is a 5- to 7-membered ring optionally having substituent(s).

As the 5- to 7-membered ring represented by ring B, a 5- to 7-membered ring optionally containing, besides carbon, hetero atoms selected from a nitrogen atom, an oxygen atom or a sulfur atom can be used. Particularly, a 5 to 7-membered carbon ring is preferable.

Particularly, as



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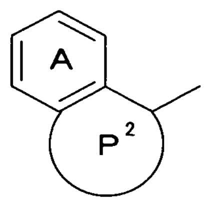

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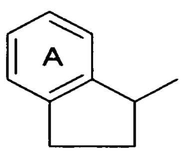

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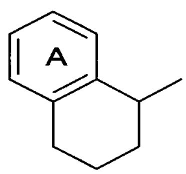

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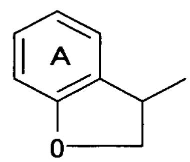
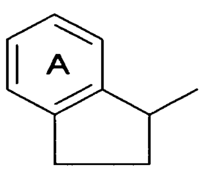


is preferable, and



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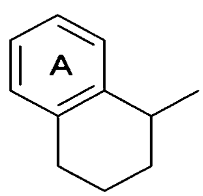


is more preferable.

As the substituent that the 5- to 7-membered ring represented by ring B may have, those similar to the above-mentioned substituent that ring P may have can be used.

Ring P^3 is an aromatic ring having substituent(s) having a benzene ring.

As the aromatic ring represented by ring P^3, those similar to the aromatic ring represented by ring P can be used, and particularly, a benzene ring is preferable.

Ring S^1 is a benzene ring having substituent(s) having a benzene ring.

As the "substituent(s) having a benzene ring" that the aforementioned aromatic ring represented by ring P^3 and the aforementioned benzene ring represented by ring S have, for example, a substituent represented by the formula: R^{11}-E- (R^{11} is a phenyl group optionally having substituent(s), and E is a bond or a spacer) and the like can be used.

As the "substituent" of the "phenyl group" represented by R^{11}, a substituent selected from the aforementioned substituent group A can be used.

As R^{11}, for example, a phenyl group optionally having substituent(s) selected from the group consisting of a halogen atom and an optionally halogenated C_{1-6} alkyl is preferable.

E is defined as above, and as E, a bond, -O- or $-CH_2-O-$ is preferable.

Ring C is a benzene ring optionally further having substituent(s) besides a -Y-COOH group.

As the substituent that the benzene ring represented by ring C may have besides -Y-COOH, those similar to the above-mentioned substituent that ring P may have can be used.

A is a substituent (except a hydrogen atom and a chlorine atom).

As the substituent (except a hydrogen atom and a chlorine atom) represented by A, a substituent selected from the aforementioned substituent group A (except a chlorine atom and a C_{1-3} alkylenedioxy) can be used, and particularly, a bromine atom is preferable.

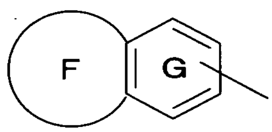
Ring D is a benzene ring further having substituent(s) (except a nitro group and a hydroxy group) besides A.

As the substituent (except a nitro group and a hydroxy group) that the benzene ring represented by ring D may have besides A, a substituent selected from the aforementioned substituent group A (except a nitro group and a hydroxy group) can be used.

Ring E is a phenylene group optionally having substituent(s), and those similar to the "phenylene group optionally having substituent(s)" represented by ring R can be used. However, no substituent is present at the position represented by -H.

Ring F is a ring optionally having substituent(s), and those similar to the "ring optionally having substituent(s)" represented by ring P^1 can be used.

Ring G is a benzene ring optionally having substituent(s), and those similar to the "benzene ring optionally having substituent(s)" represented by ring A can be used.



is not an unsubstituted naphthyl group, an unsubstituted 1H-indazolyl group and a quinolyl group optionally having substituent(s).

Ring H is a 5-membered ring optionally having substituent(s).

As the 5-membered ring represented by ring H, a 5-membered carbon ring or heterocycle can be used.

As the 5-membered carbon ring, cyclopentane and the like can be used.

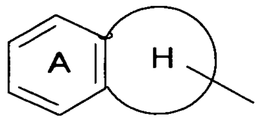
As the 5-membered heterocycle, for example, a 5-membered heterocycle containing, besides carbon atom, 1 or 2 kinds of 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom and the like can be used. Specifically, thiophene, dihydrothiophene, furan, dihydrofuran, thiazole, isothiazole, oxazole, isoxazole, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrrolidine, imidazoline, pyrazolidine, pyrazoline, oxadiazole, thiadiazole and the like can be mentioned.

As the ring H, thiophene, pyrrole and the like are

preferable.

As the substituent that the 5-membered ring represented by ring H may have, those similar to the above-mentioned substituent that ring P may have can be used.

As



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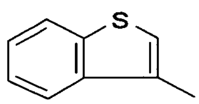
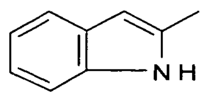


or



and the like can be preferable used.

J is -O-, -S-, $-CH_2-$ or $-NR^{12}-$ (R^{12} is a C_{1-6} alkyl group).

As the C_{1-6} alkyl group represented by R^{12}, methyl, chloromethyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl and hexyl can be used.

K is a bond or a C_{1-3} alkylene group.

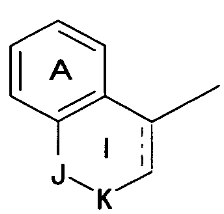
As the C_{1-3} alkylene group represented by K, methylene, ethylene and propylene can be used.

As K, a bond and methylene are preferable.

is a single bond or a double bond.

As the substituent that ring I may have, those similar to the substituent selected from the aforementioned substituent group A can be used.

As



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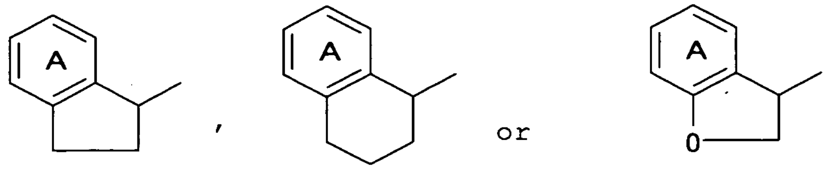


and the like are preferable. As the substituent for ring A in this case, (i) a halogen atom, (ii) a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl), (iii) a C_{1-6} alkoxy group (e.g., methoxy, ethoxy), (iv) a C_{6-14} aryl group (e.g., phenyl, naphthyl) optionally having substituent(s) selected from a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom) and a C_{1-6} alkyl (e.g., methyl, ethyl, propyl), (v) a C_{6-14} aryloxy group (e.g., phenyloxy) and (vi) a C_{7-15} aralkyloxy group (e.g., naphthyloxy), are preferable, and as the substituent of ring R, a halogen atom (e.g., fluorine atom, chlorine atom, bromine atom) is preferable.

Of the compounds used in the present invnetion compound (II), compound (IIa), compound (IIb), compound (III), compound (IV), compound (IVa), compound (IVb), compound (A), compound (B), compound (C) and compound (D) are novel.

A compound (IIb) wherein the spacer represented by X is a methylene group optionally having substituent(s), -O- or -S-; the spacer represented by Y is a C_{1-6} alkylene group optionally having substituent(s), -N-Y^1- (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)), -O-Y^1- (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)) or -S-Y^1- (Y^1 is a C_{1-6} alkylene group optionally having substituent(s)); and ring B is a 5 to 7-membered carbon ring, is preferable.

A compound (IVa) wherein ring P^3 is a benzene ring having "the substituent having a benzene ring" represented by the formula: R^{11}-E- (R^{11} is a phenyl group optionally having substituent(s), and E is a bond or a spacer) is preferable. As E, a bond, -O- or -CH_2-O- is preferable. As R^{11}, a phenyl

group optionally having substituent(s) selected from a halogen atom and an optionally halogenated C_{1-6} alkyl is preferable.

As X^1, a C_{1-6} alkylene group (particularly, a methylene group) optionally having substituent(s) such as a C_{1-6} alkyl, a C_{6-14} aryl and the like is preferable.

As W^5, a bond is preferable.

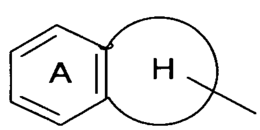
As Y^1, a C_{1-6} alkylene group (particularly, an ethylene group) optionally having substituent(s) is preferable.

As ring R, a phenylene group optionally having a C_{1-6} alkoxy is preferable.

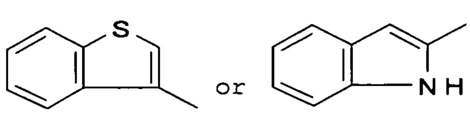
A compound (IVb) wherein ring S^1 is a benzene ring having "the substituent having a benzene ring" represented by the formula: R^{11}-E- (R^{11} is a phenyl group optionally having substituent(s), and E is a bond or a spacer) is preferable. As E, a bond, -O- or $-CH_2-O-$ is preferable. As R^{11}, a phenyl group optionally having substituent(s) selected from the group consisting of a halogen atom and an optionally halogenated C_{1-6} alkyl is preferable.

A compound (A) wherein A is a bromine atom is preferable.

A compound (C) wherein

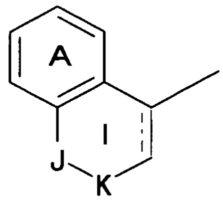


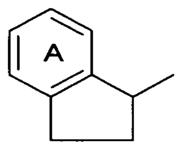
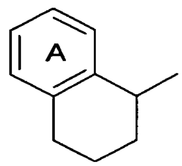
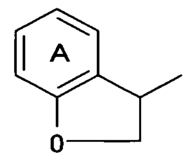
is



is preferable.

A compound (D) wherein

 is

,  or ,

and the substituent of ring A is (i) a halogen atom, (ii) a C_{1-6} alkyl group, (iii) a C_{1-6} alkoxy group, (iv) a C_{6-14} aryl group optionally having substituent(s) selected from a halogen atom and a C_{1-6} alkyl, (v) a C_{6-14} aryloxy group or (vi) a C_{7-15} aralkyloxy group, and the substituent of ring R is a halogen atom, is preferable.

Further, as the compound used in the present invention, the compounds described in JP-A-2002-265457, JP-A-2002-212171, JP-A-2001-226350, JP-A-2001-199971, JP-A-2000-198772, JP-A-2000-80086, JP-A-2000-34266, JP-A-09-323983, JP-A-08-311065 and the like can be also used.

As a salt of a compound used in the present invention, for example, metal salts, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids and the like. Preferable examples of the metal salt include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; aluminum salt, and the like. Preferable examples of the salt with organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of

the salt with inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with basic amino acid include a salt with arginine, lysin, ornithine and the like. Preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

Of these, a pharmacologically acceptable salt is preferable. For example, when the compound has an acidic functional group, inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt etc.) and the like, ammonium salt and the like are preferable, and when the compound has basic functional group, salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like; or salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and the like are preferable.

A prodrug of the compounds (I), compound (Ia), compound (Ib), compound (II), compound (IIa), compound (IIb), compound (III), compound (IV), compound (IVa), compound (IVb), compound (A), compound (B), compound (C), compound (D) and a salt thereof of the present invention (hereinafter sometimes to be abbreviated as compound (I) of the present invention) is a compound that converts to compound (I) of the present invention due to the reaction by enzyme, gastric acid and the like under the physiological conditions in the body; that is,

a compound that converts to compound (I) of the present invention by enzymatic oxidation, reduction, hydrolysis and the like, and a compound that converts to compound (I) of the present invention by hydrolysis and the like by gastric acid and the like.

Examples of a prodrug of compound (I) of the present invention include a compound wherein an amino group of compound (I) of the present invention is acylated, alkylated or phosphorylated (e.g., compound where amino group of compound (I) of the present invention is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated and the like); a compound wherein a hydroxy group of compound (I) of the present invention is acylated, alkylated, phosphorylated or borated (e.g., a compound where a hydroxy group of compound (I) of the present invention is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated and the like); a compound wherein a carboxyl group of compound (I) of the present invention is esterified or amidated (e.g., a compound where a carboxyl group of compound (I) of the present invention is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, ethoxycarbonyloxyethyl esterified, phthalizyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, cyclohexyloxycarbonylethyl esterified, methylamidated and the like) and the like. These compounds can be produced from compound (I) of the present invention by a method known *per se*.

A prodrug of compound (I) of the present invention may be a compound that converts to compound (I) of the present invention under physiological conditions as described in IYAKUHIN NO KAIHATSU, vol. 7, BUNSHI SEKKEI, 163-198, Hirokawa

Shoten (1990).

Hereinafter the production methods of the compound or a salt thereof of the present invention are explained.

The production methods of compound (II), compound (IIa), compound (IIb), compound (III), compound (IV), compound (IVa) and compound (IVb) of the present invention are described in the following.

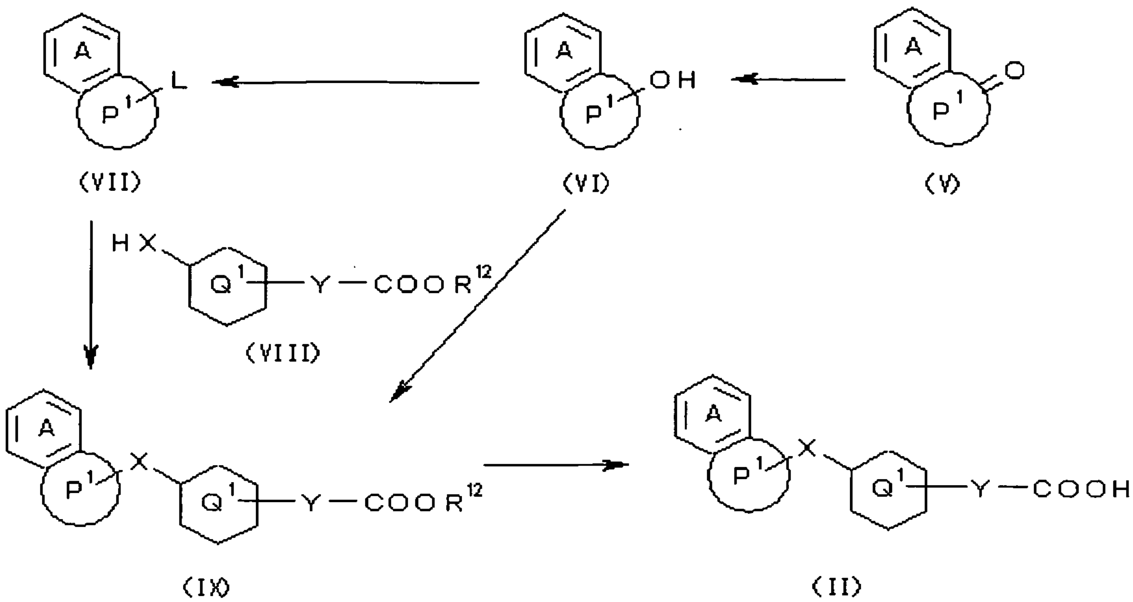
Each symbol of the compounds in the schematic drawings of the following reaction schemes is as defined above unless otherwise specified. The compound in the reaction schemes include salts, and as such salts, for example, those similar to the salts of the above-mentioned compounds to be used in the present invention and the like can be mentioned.

The resulting products can be used for the next reaction in the form of a reaction mixture or as a crude product. They can also be isolated from the reaction mixture by conventional methods, and can be easily purified by separation means such as recrystallization, distillation, chromatography and the like.

The compound (II) of the present invention can be produced by, for example, by the method shown in the following Reaction Scheme 1 or a method analogous thereto. The compounds (IIa), (IIb) and (III) can be produced according to the method of compound (II).

For compounds (V), (VI), (VII) and (VIII), commercially available ones can be easily obtained, or they can be also produced by a method known *per se* or a method analogous thereto.

Reaction Scheme 1



The compound (VI) can be produced by reducing the carbonyl group of compound (V).

As a reducing agent to be used for the reduction, for example, metal hydrides such as aluminum hydride, diisobutylaluminum hydride, tributyltin hydride and the like, metal hydride complex compounds such as lithium aluminum hydride, sodium borohydride and the like, borane complexes such as a borane tetrahydrofuran complex, a borane dimethyl sulfide complex and the like, alkylboranes such as thexylborane, disiamylborane and the like, metals such as diborane, zinc, aluminum, tin, iron and the like, alkali metal (e.g., sodium, lithium and the like)/liquid ammonia (Birch reduction) and the like can be mentioned. The amount of the reducing agent to be used is, for example, about 1 to about 10 mol, preferably about 1 to about 5 mol, per 1 mol of compound (V) in the case of metal hydrides or metal hydride complex compounds, about 1 to about 10 mol, preferably about 1 to about 5 mol, per 1 mol of compound (V) in the case of borane complexes, alkylboranes or diborane, and about 1 to about 20 equivalent, preferably about 1 to about 5 equivalent in the case of metals. In this reaction, a Lewis acid may be used when desired. As the "Lewis acid", for example, aluminum

chloride, aluminum bromide, titanium (IV) chloride, tin (II) chloride, zinc chloride, boron trichloride, boron tribromide, boron trifluoride and the like can be used. The amount of the Lewis acid to be used is about 1 to about 10 mol, preferably about 1 to about 5 mol, per 1 mol of compound (V).

In addition, reduction can be performed by hydrogenation reaction, and in this case, for example, catalysts such as palladium carbon, platinum oxide (IV), Raney-nickel, Raney-cobalt and the like, and the like can be used. The amount of the catalyst to be used is about 5 to about 1000 wt%, preferably about 10 to about 300 wt%, per 1 mol of compound (V). Various hydrogen sources can be also used instead of the gaseous hydrogen. As the "hydrogen sources", formic acid, ammonium formate, triethylammonium formate, sodium phosphinate, hydrazine and the like can be used. The amount of the hydrogen sources to be used is about 1 to about 10 mol, preferably about 1 to about 5 mol, per 1 mol of compound (V).

This reaction is advantageously carried out in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds, but a solvent, for example, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like, ethers such as diethyl ether, diisopropy ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like, organic acids such as formic acid, acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid and the like, and the like, a mixed solvent thereof and the like are preferable.

While the reaction time varies depending on the kind and amount of the reducing agent to be used or activity and amount of catalyst, it is generally about 1 hr to about 100 hr, preferably about 1 hr to about 50 hr. The reaction

temperature is generally about -20 to about 120 °C, preferably about 0 to about 80°C. When a hydrogenating catalyst is used, the pressure of hydrogen is generally about 1 to about 100 atm.

The compound (VII) wherein L is a leaving group can be produced by converting the hydroxy group of compound (VI) to a "leaving group".

As the "leaving group" represented by L, for example, a halogen atom such as fluorine, chlorine, bromine, iodine and the like, an optionally halogenated C_{1-6} alkylsulfonyloxy group such as methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy and the like, a C_{6-10} arylsulfonyloxy group optionally having substituent(s) and the like can be mentioned. As the "C_{6-10} arylsulfonyloxy group optionally having substituent(s)", for example, a C_{6-10} arylsulfonyloxy group (e.g., phenylsulfonyloxy, naphthylsulfonyloxy and the like) optionally having 1 to 3 substituent selected from a C_{1-6} alkyl group (e.g., methyl, ethyl and the like), a C_{1-6} alkoxy group (e.g., methoxy, ethoxy and the like) and nitro, and the like can be mentioned, and specific examples include phenylsulfonyloxy, m-nitrophenylsulfonyloxy, p-toluenesulfonyloxy and the like can be mentioned.

When the "leaving group" represented by L is a halogen atom, as a halogenating agent to be used for halogenation, for example, thionyl halides such as thionyl chloride, thionyl bromide and the like, phosphoryl halides such as phosphoryl chloride, phosphoryl bromide and the like, phosphorus halides such as phosphorus pentachloride, phosphorus trichloride, phosphorous pentabromide, phosphorus tribromide and the like, oxalyl halides such as oxalyl chloride and the like, phosgene and the like can be mentioned. A halogenating agent is used in a proportion of about 0.1 to about 30 mol, preferably about 0.2 to about 10 mol per 1 mol of compound (VI).

When desired, this reaction is carried out in the

presence of a base. As the "base", tertiary amines such as triethylamine, tripropylamine, tributylamine, N-ethyldiisopropylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like, and the like can be mentioned, which is used in about 1 to about 20 mol, preferably about 1 to about 10 mol, per 1 mol of compound (VI).

This reaction is advantageously carried out without solvent or in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds, but a solvent, for example, hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like, ethers such as diethyl ether, diisopropy ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, and the like, a mixed solvent thereof and the like are preferable.

The reaction time is generally about 10 min to about 12 hr, preferably about 10 min to about 5 hr. The reaction temperature is generally about -10 to about 200°C, preferably about -10 to about 120°C.

When the "leaving group" represented by L is an optionally halogenated C_{1-6} alkylsulfonyloxy group or a C_{6-10} arylsulfonyloxy group optionally having substituent(s), as the sulfonylating agent, for example, halogenated C_{1-6} alkylsulfonyl (e.g., methanesulfonyl chloride and the like), halogenated C_{6-10} arylsulfonyl (e.g., benzenesulfonyl chloride, p-toluenesulfonyl chloride and the like), and the like can be mentioned. The sulfonylating agent is used in about 1 to about 20 mol, preferably about 1 to about 10 mol, per 1 mol of compound (VI).

This reaction is advantageously carried out without solvent or in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds, but a solvent, for example, hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like, ethers such as diethyl ether, diisopropy ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, esters such as methyl acetate, ethyl acetate, butyl acetate and the like, and the like, a mixed solvent thereof and the like are preferable.

This reaction is carried out in the presence of a base when desired. As the "base", tertiary amines such as triethylamine, tripropylamine, tributylamine, N-ethyldiisopropylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like, inorganic bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide and the like, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, sodium acetate, ammonium acetate and the like, and the like can be mentioned. The base is used in about 1 to about 20 mol, preferably about 1 to about 10 mol, per 1 mol of compound (VI).

The reaction time is generally about 10 min to about 12 hr, preferably about 10 min to about 5 hr. The reaction temperature is generally about -30 to about 150°C, preferably about -20 to about 100°C.

The compound (IX) wherein R^{12} is a hydrocarbon group optionally having substituent(s) and Xa is an oxygen atom or a sulfur atom, can be produced by condensing compound (VII) with compound (VIII) in the presence of a base.

As the "hydrocarbon group optionally having

substituent(s)" represented by R^{12}, "optionally substituted lower(C_{1-6}) alkyl", "optionally substituted lower(C_{2-6}) alkenyl", "optionally substituted lower(C_{2-6}) alkynyl", "optionally substituted lower(C_{2-6}) alkynyl", "optionally substituted C_{3-8} cycloalkyl", "optionally substituted C_{6-14} aryl", "optionally substituted C_{7-16} aralkyl" and the like of the above-mentioned substituent group A are preferable.

As the substituent that the "hydrocarbon group" of the "hydrocarbon group optionally having substituent(s)" represented by R^{12} may have, the above-mentioned substituent group A and the like are preferable. The "hydrocarbon group" of the "hydrocarbon group optionally having substituent(s)" represented by R^4 may have 1 to 5, preferably 1 to 3 substituents mentioned above at substitutable position(s) of the hydrocarbon group. When the number of substituents is not less than 2, respective substituents may be the same or different.

As the base to be used for this reaction, inorganic bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide and the like, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, sodium acetate, ammonium acetate and the like, aromatic amines such as pyridine, lutidine and the like, tertiary amines such as triethylamine, tripropylamine, tributylamine, N-ethyldiisopropylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine and the like, alkali metal hydrides such as sodium hydride, potassium hydride and the like, metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide and the like, metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like, and the like can be mentioned.

This reaction is advantageously carried out using a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds, but a solvent, for example, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like, ethers such as diethyl ether, diisopropy ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, nitriles such as acetonitrile, propionitrile and the like, esters such as methyl acetate, ethyl acetate, butyl acetate and the like, sulfoxides such as dimethyl sulfoxide and the like, water and the like, mixed solvent thereof and the like are preferable.

The reaction time is generally about 10 min to about 12 hr, preferably about 20 min to about 6 hr. The reaction temperature is generally about -50 to about 150°C, preferably about -20 to about 100°C.

The compound (IX) wherein X is an oxygen atom or a sulfur atom can be also produced by condensing compound (VI) with compound (VIII) in the presence of a dehydrating agent when desired.

As the dehydrating agent usable for this reaction, for example, acidic catalysts such as hydrochloric acid, sulfuric acid, phosphoric acid, potassium hydrosensulfate, oxalic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, borone trifluoride ether complex and the like, basic catalysts such as sodium hydroxide, potassium hydroxide and the like, and the like can be mentioned, further, for example, carbodiimides such as N,N'-dicyclohexylcarbodiimide and the like, alumina, sodium dioxide, phosphorus oxychloride, thionyl chloride,

methanesulfonylchloride and the like may be used. These acid and base are used in about 0.1-10 mol, preferably about 0.1-5.0 mol, per 1 mol of compound (VIII).

This reaction is advantageously carried out without solvent or in a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, a solvent, for example, alcohols such as methanol, ethanol, propanol and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like, organic acids such as formic acid, acetic acid and the like, hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, sulfoxides such as dimethyl sulfoxide and the like, and the like, a mixed solvent thereof and the like are preferable.

The reaction time is generally 30 min-24 hr, preferably 30 min-5 hr. The reaction temperature is generally 0-200°C, preferably 0-150°C.

The compound (IX) wherein X is an oxygen atom can be also produced by condensing compound (VI) with compound (VIII) by Mitsunobu reaction (Synthesis, 1981, 1-27).

For this reaction, compound (VIII) is reacted with compound (VI) in the presence of azodicarboxylates such as diethyl azodicarboxylate, diisopropyl azodicarboxylate, 1,1'-(azodicarbonyl)dipiperidine and the like, and the like and phosphines such as triphenylphosphine, tributylphosphine and the like.

The amount of compound (VI) to be used is about 1 to about 5 mol, preferably about 1 to about 2 mol, relative to 1 mol of compound (VIII).

The amount of the "azodicarboxylates" and "phosphines" to be used is about 1 to about 5 mol, preferably about 1 to about 2 mol, relative to 1 mol of compound (VIII), respectively.

This reaction is advantageously carried out using a

solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds, but a solvent, for example, ethers such as diethyl ether, diisopropy ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, nitriles such as acetonitrile, propionitrile and the like, ketones such as acetone, ethyl methyl ketone and the like, sulfoxides such as dimethyl sulfoxide and the like, and the like, a mixed solvent thereof and the like are preferable.

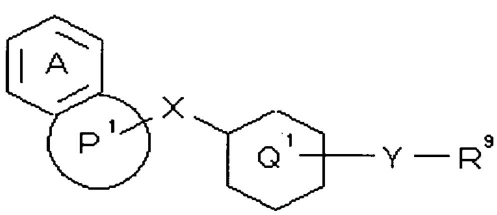
The reaction time is generally about 5 min to about 48 hr, preferably about 10 min to about 24 hr. The reaction temperature is generally about -20 to about 200°C, preferably about 0 to about 100°C.

The compound (II) is produced by hydrolyzing the ester group of compound (IX) using an acid or a base. For acid hydrolysis, mineral acids such as hydrochloric acid, sulfuric acid and the like, Lewis acids such as boron trichloride, boron tribromide and the like, Lewis acid and thiol or sulfide in combination, organic acids such as trifluoroacetic acid, p-toluenesulfonic acid and the like can be generally used. For alkaline hydrolysis, inorganic bases such as sodium hydroxide, potassium hydroxide, barium hydroxide and the like, basic salts such as sodium carbonate, potassium carbonate and the like, metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like, organic bases such as triethylamine, imidazole, formamidine and the like, and the like can be used. These acid and base are used in about 0.5-10 mol, preferably about 0.5-6 mol, per 1 mol of compound (IX).

This reaction is advantageously carried out without solvent or in a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds, but a solvent, for example, alcohols such as methanol, ethanol, propanol and the like, aromatic hydrocarbons such as benzene, toluene and the like, saturated hydrocarbons such as cyclohexane, hexane and the like, organic acids such as formic acid, acetic acid and the like, ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, nitriles such as acetonitrile, propionitrile and the like, ketones such as acetone, methyl ethyl ketone and the like, sulfoxides such as dimethyl sulfoxide and the like, water and the like, a mixed solvent thereof and the like are preferable.

The reaction time is generally 10 min-60 hr, preferably 10 min-12 hr. The reaction temperature is generally -10-200°C, preferably 0-120°C.

The compound (II) can be produced from compound (IIc) by a method similar to the method of producing compound (II) from compound (IX), that is, compound (II) can be produced by subjecting a represented by the formula



(IIc)

wherein R^9 is a cyano group or $-COR^{10}$ (R^{10} is an optionally substituted amino group, an optionally substituted C_{1-6} alkoxy group, an optionally substituted C_{6-14} aryloxy group or an optionally substituted C_{7-16} aralkyloxy group, and the other symbols are defined above, or a salt thereof to hydrolysis.

As the "optionally substituted amino group" for R^{10}, those similar to the "optionally substituted amino group" in the

above-mentioned Group A can be mentioned.

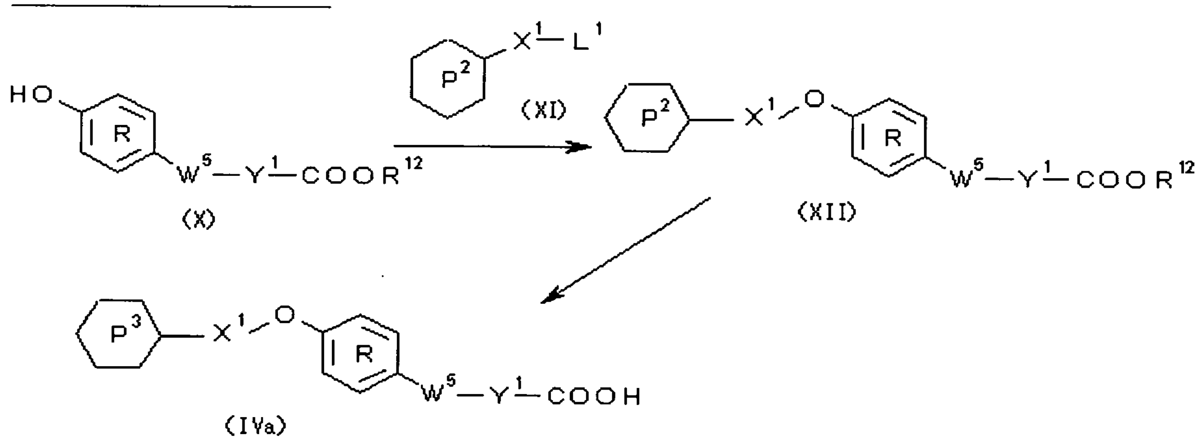
As the "optionally substituted C_{1-6} alkoxy group" for R^{10}, those similar to the "optionally substituted lower (C_{1-6}) alkoxy group" in the above-mentioned Group A can be mentioned.

As the "optionally substituted C_{6-14} aryloxy group" for R^{10}, those similar to the "optionally substituted C_{6-14} aryloxy group" in the above-mentioned Group A can be mentioned.

As the "optionally substituted C_{7-16} aralkyloxy group" for R^{10}, those similar to the "optionally substituted C_{7-16} aralkyloxy group" in the above-mentioned Group A can be mentioned.

The compound (IVa) of the present invention can be produced by, for example, the method represented by the following Reaction Scheme 2 or a method analogous thereto. In addition, compound (IV) and (IVb) can be produced by a method similar to the method of producing compound (IVa).

Reaction Scheme 2



For compounds (X) and (XI), commercially available ones can be easily obtained, or they can be also produced by a method known *per se* or a method analogous thereto.

The compound (XII) can be produced by condensing compound (X) with compound (XI) wherein L^1 is a leaving group.

As the "leaving group" represented by L^1, those similar to the aforementioned "leaving group" represented by L, a hydroxy group and the like can be mentioned.

When the "leaving group" represented by L^1 is a hydroxy

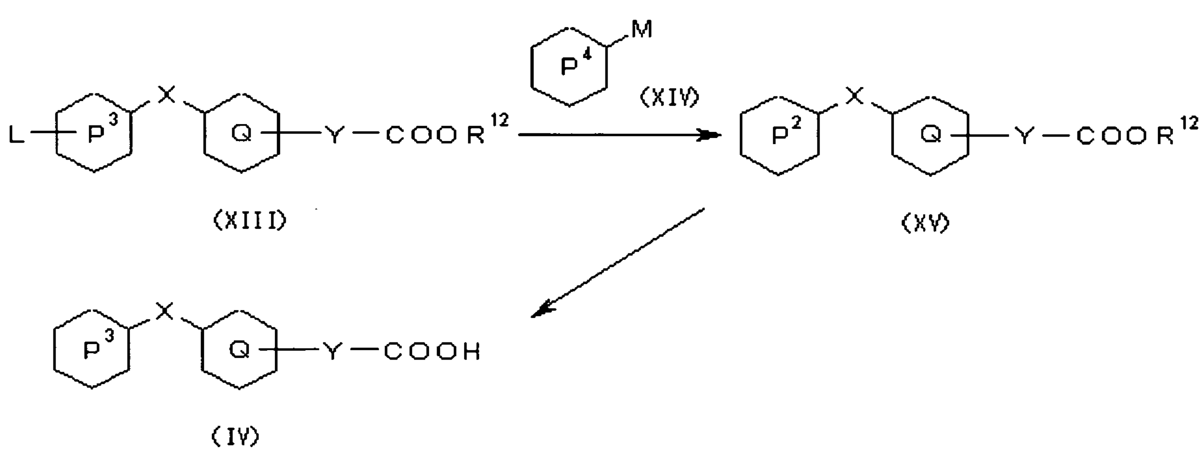
group, compound (XII) can be produced from compound (X) and compound (XI) by a method similar to the method of producing compound (IX) from compound (VI).

When the "leaving group" represented by L^1 is a halogen atom, an optionally halogenated C_{1-6} alkylsulfonyloxy group or a C_{6-10} arylsulfonyloxy group optionally having substituent(s), compound (XII) can be produced from compound (X) and compound (XI) by a method similar to the method of producing compound (IX) from compound (VII).

The compound (IVa) can be produced from compound (XII) by a method similar to the method of producing compound (II) from compound (IX).

The compound (IV) of the present invention can be also produced by, for example, the method represented by the following Reaction Scheme 3 or a method analogous thereto. In addition, compound (IVa) and (IVb) can be produced by a method similar to the method of producing compound (IV).

Reaction Scheme 3



For compounds (XIII) and (XIV), commercially available ones can be easily obtained, or they can be also produced by a method known *per se* or a method analogous thereto.

The compound (XV) can be produced by condensing compound (XIII) (wherein P^3 is an aromatic ring optionally further having substituent(s) besides L) with compound (XIV) (wherein M is a metal and P^3 is a benzene ring optionally further having,

besides M, substituent(s) or an aromatic ring further having, besides M, substituent(s) having a benzene ring).

As the "aromatic ring optionally having substituent(s)" represented by P^3, those similar to ring P^2 and the like can be mentioned. As the "metal" represented by M, potassium, sodium, lithium, magnesium, mercury, zinc, thallium, tin, boron and the like can be mentioned. They may be in the form of complex.

As the substituent that the "benzene ring optionally having substituent(s)" represented by P^4 may have, a substituent selected from the above-mentioned substituent group A and the like can be mentioned.

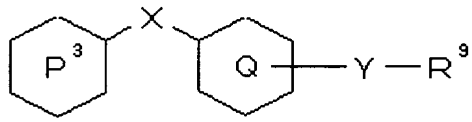
This reaction is advantageously carried out in the presence of a catalyst when desired. As the "catalyst", nickel complex, palladium complex, copper and the like can be mentioned. The catalyst is used in about 0.005 to about 2 mol, preferably about 0.01 to about 1 mol, per 1 mol of compound (XIII).

This reaction is advantageously carried out using a solvent inert to the reaction. Such solvent is not particularly limited as long as the reaction proceeds, but a solvent, for example, hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like, ethers such as diethyl ether, diisopropy ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, and the like, a mixed solvent thereof and the like are preferable.

The reaction time is generally about 10 min to about 48 hr, preferably about 10 min to about 24 hr. The reaction temperature is generally about -80 to about 250°C, preferably about -20 to about 150°C.

The compound (IV) can be also produced from compound (XV) by a method similar to the method of producing compound (II) from compound (IX).

In addition, compound (IV) can also be produced from compound (IVc) by a method similar to the method of producing compound (II) from compound (IX), that is, compound (IV) can be produced by subjecting a represented by the formula



(IVc)

wherein each symbol is as defined above, or a salt thereof to hydrolysis.

In each of the aforementioned reactions, when the starting compound has amino group, a carboxyl group or hydroxy group as a substituent, a protecting group generally used in peptide chemistry and the like may be introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained.

As the amino-protecting group, for example, formyl, or C_{1-6} alkyl-carbonyl (e.g., acetyl, prpionyl and the like), benzoyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl and the like), phenyloxycarbonyl, C_{7-10} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl and the like), trityl or phthaloyl, each of which optionally has substituent(s), can be mentioned. As the substituent, a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, valeryl and the like), nitro and the like can be used. The number of the substituent is about 1 to 3.

As the carboxy-protecting group, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), phenyl, trityl or silyl and the like, each of which optionally has substituent(s), can be mentioned. As the substituent, a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, butylcarbonyl and the like), nitro, C_{1-6} alkyl (e.g., methyl, ethyl, tert-butyl and the like), C_{1-6} aryl (e.g., phenyl,

naphthyl and the like) and the like can be used. The number of the substituent is about 1 to 3.

As the hydroxy-protecting group, for example, formyl, or C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), phenyl, C_{7-10} aralkyl (e.g., benzyl and the like), C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl and the like), phenyloxycarbonyl, C_{7-10} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl and the like), tetrahydropyranyl, tetrahydrofuranyl or silyl and the like, each of which optionally has substituent(s), can be mentioned. As the substituent, a halogen atom (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkyl (e.g., methyl, ethyl, tert-butyl and the like), C_{7-10} aralkyl (e.g., benzyl and the like), C_{6-10} aryl (e.g., phenyl, naphthyl and the like), nitro and the like can be used. The number of the substituent is about 1 to 4.

For elimination of the protecting group, a method known *per se* or a method analogous thereto is used. For example, treatment method with acid, base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium (II) acetate and the like or reductive reaction can be used.

In any case, further if necessary, compound (II), compound (IIa), compound (IIb), compound (III), compound (IV), compound (IVa) and compound (IVb) can be synthesized by using known deprotection reactions, acylation reactions, alkylation reactions, hydrogenation reactions, oxidation reactions, reduction reactions, carbon chain extension reactions, substituent exchange reactions, each alone or in combination of two or more of them. As these reactions, for example, methods described in SHINJIKKEN KAGAKU KOUZA 14, vol. 15, 1977 (Maruzen Press), etc. are adopted.

The compound (A), compound (B), compound (C) and compound (D) can also be produced by a method similar to the

above-mentioned method.

The compounds to be used in the present invention can be produced by the above-mentioned production methods and the methods described in JP-A-2002-265457, JP-A-2002-212171, JP-A-2001-226350, JP-A-2001-199971, JP-A-2000-198772, JP-A-2000-80086, JP-A-2000-34266, JP-A-09-323983, JP-A-08-311065 and the like.

When the intended substance is obtained in the free form by the above-mentioned reaction, it may be converted into a salt according to an ordinary method, while when obtained in the form of a salt, it can also be converted into a free form or other salt according to an ordinary method. Thus obtained compound or a salt thereof can be isolated and purified from a reaction solution by known means, for example, rolling, concentration, solvent extraction, fractionation, crystallization, recrystallization, chromatography and the like.

When compound of the present invention is present as a configurational isomer (stereoisomer), diastereomer, conformer or the like, each can be isolated by the above separation and purification methods on demand. In addition, when compound of the present invention is in the form of racemates, they can be separated into S- and R-forms by any conventional optical resolution.

When compound of the present invention includes stereoisomers, both the isomers alone and mixtures of each isomers are included in the scope of the present invention.

In addition, compound of the present invention may be a hydrate or non-hydrate.

The compound of the present invention may be labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S and the like) or the like.

The GPR40 receptor function regulating action of the compounds of the present invention can be determined by the method described in Experimental Example 4 to be mentioned

later or a method analogous thereto.

The compound of the present invention and a prodrug thereof (hereinafter sometimes to be abbreviated as the compound of the present invention) show an action to alter bindability between a fatty acid, which is a ligand, and a GPR40 receptor, particularly GPR40 receptor agonist activity, and show low toxicity and a fewer side effects. Therefore, they are useful as a safe GPR40 receptor function regulator, preferably GPR40 agonist.

A pharmaceutical composition containing the compound of the present invention shows a superior GPR40 receptor function regulating action in mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.), and is useful as a modulator of physiological function in which GPR40 receptor is involved or an agent for the prophylaxis or treatment of disease state or disease in which GPR40 receptor is involved.

To be specific, the pharmaceutical composition containing the compound of the present invention is useful as an insulin secretion modulator (preferably insulin secretagogue) and pancreatic β cell protector.

Moreover, the pharmaceutical composition containing the compound of the present invention is useful as an agent for the prophylaxis or treatment of diseases such as diabetes, impaired glucose tolerance, ketosis, acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hyperlipidemia, genital disorder, skin disease, arthropathy, osteopenia, arteriosclerosis, thrombotic disease, dyspepsia, memory and learning disorder, obesity, hypoglycemia, hypertension, edema, insulin resistance, unstable diabetes, fatty atrophy, insulin allergy, insulinoma, lipotoxicity, cancer and the like, particularly, diseases such as diabetes, impaired glucose tolerance, ketosis, acidosis, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hyperlipidemia, genital disorder, skin disease, arthropathy,

osteopenia, arteriosclerosis, thrombotic disease, dyspepsia, memory and learning disorder and the like. Here, diabetes includes insulin-dependent (type I) diabetes and non-insulin-dependent (type II) diabetes can be mentioned.

The pharmaceutical composition comprising the compound of the present invention shows low toxicity and can be safely administered orally or parenterally (e.g., topical, rectal, intravenous administration etc.) as a pharmaceutical preparation of the compound of the present invention as it is or after admixing with a pharmacologically acceptable carrier to give, for example, tablet (including sugar-coated tablet and film-coated tablet), powder, granule, capsules (including soft capsules), liquid, injection, suppository, sustained-release preparation and the like, according to a methods known *per se* used for the general production method for pharmaceutical preparations.

The content of the compound of the present invention in the preparation of the present invention is about 0.01 to about 100% by weight relative to the whole preparation. The dose varies depending on administration subjects, administration route, diseases, condition and the like. When the compound is orally administered to a patient with diabetes (body weight about 60 kg), the dose is about 0.01 to about 30 mg/kg body weight per day, preferably about 0.1 to about 20 mg/kg body weight per day, more preferably about 1 to about 20 mg/kg body weight per day, as an active ingredient [the compound of the present invention], which may be given at once or in several portions a day.

As pharmacologically acceptable carriers that can be used for the production of the pharmaceutical agent of the present invention, various organic or inorganic carriers conventionally used as materials for pharmaceutical preparations can be mentioned. For example, excipient, lubricant, binder and disintegrant for solid preparations; and solvent, dissolution

aids, suspending agent, isotonizing agent, buffer and soothing agent and the like for liquid preparations can be mentioned. Where necessary, conventional additives such as preservative, antioxidant, coloring agent, sweetening agent, adsorbing agent, wetting agent and the like can be used.

As the excipient, for example, lactose, sucrose, D-mannitol, starch, corn starch, crystalline cellulose, light silicic anhydride and the like can be mentioned.

As the lubricant, for example, magnesium stearate, calcium stearate, talc, colloidal silica and the like can be mentioned.

As the binder, for example, crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methylcellulose, carboxymethylcellulose sodium and the like can be mentioned.

As the disintegrant, for example, starch, carboxymethylcellulose, carboxymethylcellulose calcium, carboxymethylstarch sodium, L-hydroxypropylcellulose and the like can be mentioned.

As the solvent, for example, water for injection, alcohol, propyleneglycol, macrogol, sesame oil, corn oil, olive oil and the like can be mentioned.

As the dissolution aids, for example, polyethylene glycol, propyleneglycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like can be mentioned.

As the suspending agent, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose,

hydroxypropylcellulose and the like, and the like can be mentioned.

As an isotonizing agent, for example, glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol and the like can be mentioned.

As the buffer, for example, buffers such as phosphate, acetate, carbonate, citrate and the like, and the like can be mentioned.

As the soothing agent, for example, benzyl alcohol and the like can be mentioned.

As the preservative, for example, p-hydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like can be mentioned.

As the antioxidant, for example, sulfite, ascorbic acid, α-tocopherol and the like can be mentioned.

Furthermore, the compound of the present invention can be used in combination with a drug other than the compound of the present invention.

As the drug that can be used in combination with the compound of the present invention (hereinafter sometimes to be abbreviated as concomitant drug), for example, other drug for the above-mentioned diseases (other therapeutic agents for diabetes, therapeutic agents for diabetic complications, therapeutic agent for hyperlipidemia, antiobesitic agent), chemotherapeutic agent, immunotherapeutic agent, immunomodulator, antiinflammatory drug, antibacterial agent, antifungal agent, antiprotozoal agent, antibiotic, antitussive and expectorant drug, sedative, anesthetic, antiulcer drug, therapeutic agent for arrhythmia, antihypertensive diuretic, anticoagulant drug, tranquilizer, antipsychotic, antitumor drug, muscle relaxant, anticonvulsant, antidepressant, antiallergic drug, cardiac, antiarrhythmic agent, vasodilator, vasoconstrictor, antihypertensive drug, diuretic, antinarcotic, vitamin, vitamin derivative, antiasthmatic, therapeutic agent

for incontinentia or pollakiuria, therapeutic agent for atopic dermatitis, therapeutic agent for allergic rhinitis, hypertensor, endotoxin-antagonist or -antibody, signal transduction inhibitor, inhibitor of inflammatory mediator activity, antibody to inhibit inflammatory mediator activity, inhibitor of anti-inflammatory mediator activity, antibody to inhibit anti-inflammatory mediator activity and the like. Specific examples thereof include the following.

As the other therapeutic agent for diabetes, insulin preparations (e.g., animal insulin preparations extracted from the pancreas of bovine and pig; human insulin preparations genetically synthesized using *Escherichia coli*, yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1 etc.) and the like), insulin sensitizers (e.g., Pioglitazone hydrochloride, troglitazone, Rosiglitazone maleate, JTT-501, MCC-555, YM-440, GI-262570, KRP-297, FK-614, CS-011 and the like), α-glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate etc.), biguanides (e.g., phenformin, metformin, buformin etc.), sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride etc.), other insulin secretagogues (e.g., repaglinide, senaglinide, mitiglinide or calcium salt hydrate thereof, GLP-1, nateglinide) , dipeptidyl peptidase IV inhibitor (e.g., NVP-DPP-278, PT-100, P32/98 etc.), β3 agonist (e.g., CL-316243, SR-58611-A, UL-TG-307, AJ-9677, AZ40140 etc.), amylin agonists (e.g., pramlintide etc.), phosphotyrosine phosphatase inhibitors (e.g., vanadic acid etc.), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitor, glucagon antagonist etc.), SGLT (sodium-glucose cotransporter) inhibitors (e.g., T-1095 etc.) and the like can be mentioned.

Examples of the therapeutic agent for diabetic complications include aldose reductase inhibitors (e.g.,

Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Fidarestat (SNK-860), Minalrestat (ARI-509), CT-112 etc.), neurotrophic factors (e.g., NGF, NT-3 and the like), AGE inhibitors (e.g., ALT-945, pimagedine, pyratoxanthine, N-phenacylthiazolium bromide (ALT-766), EXO-226 etc.), active oxygen scavengers (e.g., thioctic acid etc.), cerebral vasodilators (e.g., tiapride etc.).

Examples of the therapeutic agent of hyperlipidemia include statin compounds, which are cholesterol synthesis inhibitors (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin and salts thereof (e.g., sodium salt etc.) etc.), squalene synthase inhibitors, fibrate compounds (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate etc.) and the like.

Examples of the antihypertensive agent include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril etc.), angiotensin II receptor antagonists (e.g., losartan, candesartan cilexetil etc.), calcium antagonist (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine etc.), Clonidine and the like.

Examples of the antiobestic agent include antiobestic agents acting on the central nervous system (e.g., Dexfenfluramine, fenfluramine, phentermine, Sibutramine, amfepramone, dexamphetamine, Mazindol, phenylpropanolamine, clobenzorex and the like), pancreatic lipase inhibitors (e.g., orlistat etc.), β3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, AJ-9677, AZ40140 etc.), peptidic anorexiants (e.g., leptin, CNTF (Ciliary Neurotropic Factor) etc.), cholecystokinin agonists (e.g., lintitript, FPL-15849 etc.) and the like.

Examples of the diuretic include xanthine derivatives (e.g., sodium salicylate and theobromine, calcium salicylate and theobromine etc.), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide,

hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide etc.), antialdosterone preparations (e.g., spironolactone, triamterene etc.), carbonate dehydratase inhibitors (e.g., acetazolamide and the like), chlorobenzenesulfonamide preparations (e.g., chlortalidone, mefruside, indapamide etc.), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, furosemide and the like.

Examples of the chemotherapeutic agent include alkylation agents (e.g., cyclophosphamide, ifosfamide etc.), metabolic antagonists (e.g., methotrexate, 5-fluorouracil etc.), anti-cancer antibiotics (e.g., mitomycin, adriamycin etc.), plant-derived anti-cancer agents (e.g., vincristin, vindesine, taxol etc.), cisplatin, carboplatin, etoposide and the like. Of these, furtulon and neofurtulon, which are 5-fluorouracil derivatives, and the like are preferable.

Examples of the immunotherapeutic agent include microorganism or bacterial components (e.g., muramyl dipeptide derivative, picibanil etc.), polysaccharides having immunity potentiating activity (e.g., lentinan, sizofiran, krestin etc.), cytokines obtained by genetic engineering techniques (e.g., interferon, interleukin (IL) etc.), colony stimulating factors (e.g., granulocyte colony stimulating factor, erythropoietin etc.) and the like, with preference given to interleukins such as IL-1, IL-2, IL-12 and the like.

Furthermore, drugs having a cachexia-improving action established in animal models and clinical situations, such as cyclooxygenase inhibitors (e.g., Indometacin etc. [Cancer Research, vol. 49, 5935-5939, 1989], Progesterone derivatives (e.g., Megesterol acetate) [Journal of Clinical Oncology, vol. 12, 213-225, 1994], glucosteroid (e.g., dexamethasone etc.), metoclopramide agents, tetrahydrocannabinol agents (literatures are as mentioned above), fat metabolism improving agents (e.g., eicosapentaenoic acid etc.) [British Journal of Cancer, vol. 68,

314-318,1993], growth hormones, IGF-1, or antibodies to a cachexia-inducing factor such as TNF-α, LIF, IL-6, Oncostatin M and the like, can be used in combination with the compound of the present invention.

Further, glycosylation inhibitors (e.g., ALT-711, etc.), nerve regeneration promoting drugs (e.g., Y-128, VX853, prosaptide, etc.), antidepressants (e.g., desipramine, amitriptyline, imipramine, etc.), anticonvulsants (e.g., lamotrigine), antiarrhythmic drugs (e.g., mexiletine), acetylcholine receptor ligands (e.g., ABT-594), endothelin receptor antagonists (e.g., ABT-627), monoamine uptake inhibitors (e.g., tramadol), narcotic analgesics (e.g., morphine), GABA receptor agonists (e.g., gabapentin), α_2 receptor agonists (e.g., clonidine), local analgesics (e.g., capsaicin), protein kinase C inhibitors (e.g.,LY-333531), antianxiety drugs (e.g., benzothiazepines), phosphodiesterase inhibitors (e.g., sildenafil), dopamine receptor agonists (e.g., apomorphine) and the like can be also used in combination with the compound of the present invention.

By combining the compound of the present invention and a concomitant drug, a superior effect such as

(1) the dose of the compound of the present invention or a concomitant drug can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,

(2) the drug to be used in combination with the compound of the present invention can be selected depending on the condition of patients (mild, severe and the like),

(3) the period of treatment can be set longer by selecting a concomitant drug having different action and mechanism from those of the compound of the present invention,

(4) a sustained treatment effect can be designed by selecting a concomitant drug having different action and mechanism from those of the compound of the present invention,

(5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

In the following, use of the compound (I) of the present invention and a concomitant drug in combination is to be referred to as the "concomitant agent of the present invention".

For the use of the concomitant agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention and the concomitant drug can be administered to an administration subject simultaneously, or may be administered at staggered times. The dosage of the concomitant drug may be determined according to the dose clinically used, and can be appropriately selected depending on an administration subject, administration route, disease, combination and the like.

The administration mode of the concomitant agent of the present invention is not particularly restricted, as long as the compound of the present invention and the concomitant drug are combined in administration. Examples of such administration mode include the following methods: (1) The compound of the present invention and the concomitant drug are simultaneously formulated to give a single preparation which is administered. (2) The compound of the present invention and the concomitant drug are separately formulated to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the concomitant drug are separately formulated to give two kinds of preparations which are administered by the same administration route at staggered times. (4) The compound of the present invention and the concomitant drug are separately formulated to give two kinds of preparations which are administered simultaneously by the different administration routes. (5) The compound of the

present invention and the concomitant drug are separately formulated to give two kinds of preparations which are administered by the different administration routes at staggered times (for example, the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order), and the like.

A concomitant agent of the present invention has low toxicity, and for example, the compound of the present invention and/or the above-mentioned concomitant drug can be mixed, according to a method known *per se*, with a pharmacologically acceptable carrier to give pharmaceutical compositions, for example, tablets (including a sugar-coated tablet, film-coated tablet), powders, granules, capsules (including soft capsules), liquids, injections, suppositories, sustained-release preparations and the like, which can be safely administered orally or parenterally (e.g., topical, rectal, intravenous administration, and the like). An injection can be administered by intravenous, intramuscular, subcutaneous or intraorgan route, or directly to the lesion.

As a pharmacologically acceptable carrier which may be used for preparing the concomitant agent of the present invention, various organic or inorganic carriers conventionally used as materials for pharmaceutical preparations are used as a pharmacologically acceptable carrier, which are added as excipient, lubricant, binder, disintegrant for solid preparations; and solvent, dissolution aids, suspending agent, isotonicity agent, buffer, soothing agent and the like for liquid preparations, and the like can be mentioned. Further, where necessary, conventional additives such as preservative, antioxidant, coloring agent, sweetening agent, adsorbing agent, wetting agent and the like can be appropriately used in an appropriate amount.

Preferable examples of the excipient include lactose, sucrose, D-mannitol, starch, pregelatinized starch, dextrin,

crystalline cellulose, light silicic anhydride and the like.

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

Preferable examples of the binder include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone starch, saccharose, gelatin, methylcellulose, sodium carboxymethylcellulose and the like.

Preferable examples of the disintegrant include starch, carboxymethylcellulose, calcium carboxymethylcellulose, sodium carboxymethyl starch, low-substituted hydroxypropyl cellulose and the like.

Preferable examples of the solvent include water for injection, alcohol, polyethylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil and the like.

Preferable examples of the dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like.

Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and the like; and the like.

Preferable examples of the isotonicity agent include glucose, D-sorbitol, sodium chloride, glycerol, D-mannitol and the like.

Preferable examples of the buffer include phosphate buffer, acetate buffer, carbonate buffer, citrate buffer and the like.

Preferable examples of the soothing agent include benzyl alcohol and the like.

Preferable examples of the preservative include p-oxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Preferable examples of the antioxidant include sulfite, ascorbic acid, α-tocopherol and the like.

The compounding ratio of the compound of the present invention to the concomitant drug in the concomitant agent of the present invention can be appropriately selected depending on an administration subject, administration route, diseases and the like.

For example, the content of the compound of the present invention in the concomitant agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of the concomitant drug in the concomitant agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of additives such as a carrier and the like in the concomitant agent of the present invention differs depending on the form of a preparation, and usually from about 1 to 99.99% by weight, preferably from about 10 to 90% by weight, based on the preparation.

In the case when the compound of the present invention and the concomitant drug are separately prepared respectively, the same contents may be adopted.

These preparations can be produced by a method known *per se* usually used in a preparation process.

For example, the compound of the present invention and the concomitant drug can be made into an aqueous injection together with a dispersing agent (e.g., Tween 80 (manufactured by Atlas

Powder, US), HCO 60 (manufactured by Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, hydroxypropylmethylcellulose, dextrin and the like), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose and the like), a pH regulator (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl p-hydroxybenzoate, benzoic acid, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, benzyl alcohol and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a dissolution aid (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like, or can be dissolved, suspended or emulsified in a vegetable oil such as olive oil, sesame oil, cotton seed oil, corn oil and the like or a dissolution aid such as propylene glycol and molded into an oily injection.

In addition, an excipient (e.g., lactose, sucrose, starch and the like), a disintegrant (e.g., starch, calcium carbonate and the like), a binder (e.g., starch, acacia, carboxymethylcellulose, polyvinylpyrrolidone, hydroxpropylcellulose and the like), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like, for example, can be added to the compound of the present invention or the concomitant drug, according to a method known *per se*, and the mixture can be compression-molded, then if desirable, the molded product can be coated by a method known *per se* for the purpose of masking of taste, enteric property or durability, to obtain a preparation for oral administration. As this coating agent, for example,

hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (methacrylic acid·acrylic acid copolymer, manufactured by Rohm, DE), pigment (e.g., iron oxide red, titanium dioxide, etc.) and the like can be used. The preparation for oral administration may be any of a quick release preparation and a sustained release preparation.

Furthermore, the compound of the present invention and the concomitant drug can be made into an oily or aqueous solid, a semisolid or liquid suppository. As the oily base used in the above-mentioned, for example, glycerides of higher fatty acids [e.g., cacao butter, Witepsols (manufactured by Dynamite Nobel, DE), etc.], intermediate grade fatty acids [e.g., Miglyols (manufactured by Dynamite Nobel, DE), etc.], or vegetable oils (e.g., sesame oil, soy bean oil, cotton seed oil and the like), and the like are mentioned. Further, as the aqueous base, for example, polyethylene glycols, propylene glycol and the like are mentioned, and as the aqueous gel base, for example, natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like are mentioned.

As the above-mentioned sustained release preparation, sustained release microcapsules and the like are mentioned. The sustained-release microcapsule can be produced by a method known *per se*, such as the method shown in the following [2].

A compound of the present invention is preferably molded into a preparation for oral administration such as a solid preparation (e.g., powder, granule, tablet, capsule) and the like, or molded into a preparation for rectal administration such as a suppository. Particularly, a preparation for oral administration is preferable.

The concomitant drug can be made into the above-mentioned preparation form depending on the kind of the drug.

[1] An injection of the compound of the present invention or the concomitant drug, and preparation thereof, [2] a sustained release preparation or quick release preparation of the compound of the present invention or the concomitant drug, and preparation thereof, [3] a sublingual, buccal or intraoral quick integrating agent of the compound of the present invention or the concomitant drug, and preparation thereof, will be described below specifically.

[1] Injection and preparation thereof

An injection prepared by dissolving the compound of the present invention or the concomitant drug into water is preferable. This injection may be allowed to contain a benzoate and/or salicylate.

The injection is obtained by dissolving the compound of the present invention or the concomitant drug, and if desirable, a benzoate and/or salicylate, into water.

As the above-mentioned benzoate and salicylate, for example, salts of alkali metals such as sodium, potassium and the like, salts of alkaline earth metals such as calcium, magnesium and the like, ammonium salts, meglumine salts, organic acid salts such as tromethamol etc., and the like are mentioned.

The concentration of the compound of the present invention or the concomitant drug in an injection is from 0.5 to 50% (w/v), preferably from about 3 to 20% (w/v). The concentration of the benzoate or/and salicylate is from 0.5 to 50% (w/v), preferably from 3 to 20% (w/v).

Into a preparation of the present invention, additives usually used in an injection, for example, a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent

(e.g., sodium chloride, potassium chloride, and the like), a dispersing agent (e.g., hydroxypropylmethylcellulose, dextrin, and the like), a pH regulator (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl p-hydroxybenzoate, benzoic acid and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a dissolution aid (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like, can be appropriately compounded. These additives are generally compounded in a proportion usually used in an injection.

It is advantageous that pH of an injection is controlled from 2 to 12, preferably from 2.5 to 8.0 by addition of a pH regulator.

An injection is obtained by dissolving the compound of the present invention or the concomitant drug and if desirable, a benzoate and/or a salicylate, and if necessary, the above-mentioned additives into water. These may be dissolved in any order, and can be appropriately dissolved in the same manner as in a conventional method of producing an injection.

An aqueous solution for injection may be advantageously be heated, alternatively, for example, filter sterilization, high pressure heat sterilization and the like can be conducted in the same manner as for a usual injection, to provide an injection.

It may be advantageous that an aqueous solution for injection is subjected to high pressure heat sterilization at 100 to 121°C for 5 to 30 minutes.

Further, a preparation endowed with an antibacterial property of a solution may also be produced so that it can be used as a preparation which is divided and administered multiple times.

[2] Sustained release preparation or quick release preparation, and preparation thereof

A sustained release preparation is preferable which is obtained, if desirable, by coating a nucleus containing the compound of the present invention or the concomitant drug with a film agent such as a water-insoluble substance, swellable polymer and the like. For example, a sustained release preparation for oral administration for a single administration per day type is preferable.

As the water-insoluble substance used in a film agent, there are mentioned, for example, cellulose ethers such as ethylcellulose, butylcellulose and the like, cellulose esters such as cellulose acetate, cellulose propionate and the like, polyvinyl esters such as polyvinyl acetate, polyvinyl butyrate and the like, acrylic acid/methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymers, polyacrylic acid, polymethacrylic acid, methacrylic acid alkylamide copolymers, poly(methyl methacrylate), polymethacrylate, polymethacrylamide, aminoalkyl methacrylate copolymers, poly(methacrylic anhydride), glycidyl methacrylate copolymer, particularly, acrylic acid-based polymers such as Eudragits (Rohm Pharma) such as Eudragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (ethyl acrylate·methyl methacrylate·trimethyl chloride methacrylate·ammoniumethyl copolymer), Eudragit NE-30D (methyl methacrylate·ethyl acrylate copolymer), and the like, hardened oils such as hardened castor oil (e.g., Lovery wax (Freunt) and the like), waxes such as carnauba wax, fatty acid glycerin ester, paraffin and the like, polyglycerin fatty acid esters, and the like.

As the swellable polymer, polymers having an acidic dissociating group and showing pH dependent swelling are preferable, and polymers manifesting slight swelling in acidic regions such as in the stomach and greater swelling in neutral regions such as in the small intestine and the large intestine are preferable.

As such a polymer having an acidic dissociating group and showing pH dependent swelling, cross-linkable polyacrylic acid copolymers such as, for example, Carbomer 934P, 940, 941, 974P, 980, 1342 and the like, polycarbophil, calcium polycarbophil (all are manufactured by BF Goodrich), Hibiswako 103, 104, 105, 304 (all are manufactured by Wako Pure Chemical Co., Ltd.), and the like, are mentioned.

The film agent used in a sustained release preparation may further contain a hydrophilic substance.

As the hydrophilic substance, for example, polysaccharides which may contain a sulfate group such as pullulan, dextrin, alkali metal alginate and the like, polysaccharides having a hydroxyalkyl group or carboxyalkyl group such as hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium and the like, methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol and the like.

The content of a water-insoluble substance in the film agent of a sustained release preparation is from about 30 to about 90% (w/w), preferably from about 35 to about 80% (w/w), further preferably from about 40 to about 75% (w/w), the content of a swellable polymer is from about 3 to 30% (w/w), preferably from about 3 to about 15% (w/w). The film agent may further contain a hydrophilic substance, and in which case, the content of a hydrophilic substance in the film agent is about 50% (w/w) or less, preferably about 5 to about 40% (w/w), further preferably from about 5 to about 35% (w/w). This % (w/w) indicates % by weight based on a film agent composition which is obtained by removing a solvent (e.g., water, lower alcohols such as methanol, ethanol and the like) from a film agent solution.

The sustained release preparation is produced by preparing a nucleus containing a drug as exemplified below, then, coating the resulting nucleus with a film agent solution

prepared by heat-solving a water-insoluble substance, swellable polymer and the like or by dissolving or dispersing it in a solvent.

I. Preparation of nucleus containing drug

The form of nucleus containing a drug to be coated with a film agent (hereinafter, sometimes simply referred to as nucleus) is not particularly restricted, and preferably, the nucleus is formed into particles such as a granule or fine particle.

When the nucleus is composed of granules or fine particles, the average particle size thereof is preferably from about 150 to 2000 μm, further preferably, from about 500 to about 1400 μm.

Preparation of the nucleus can be effected by a usual production method. For example, a suitable excipient, binder, disintegrant, lubricant, stabilizer and the like are mixed into a drug, and the mixture is subjected to a wet extrusion granulating method, fluidized bed granulating method or the like, to prepare a nucleus.

The content of drugs in a nucleus is from about 0.5 to about 95% (w/w), preferably from about 5.0 to about 80% (w/w), further preferably from about 30 to about 70% (w/w).

As the excipient contained in the nucleus, for example, saccharides such as sucrose, lactose, mannitol, glucose and the like, starch, crystalline cellulose, calcium phosphate, corn starch and the like are used. Among them, crystalline cellulose and cornstarch are preferable.

As the binder, for example, polyvinyl alcohol, hydroxypropyl cellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum Arabic, gelatin, starch and the like are used. As the disintegrant, for example, carboxymethylcellulose calcium (ECG505), crosscarmelose sodium (Ac-Di-Sol), crosslinked polyvinylpyrrolidone (Crospovidone), low-substituted hydroxypropylcellulose (L-HPC) and the like are

used. Among them, hydroxypropylcellulose, polyvinylpyrrolidone, low-substituted hydroxypropylcellulose are preferable. As the lubricant and coagulation inhibitor, for example, talc, magnesium stearate and inorganic salts thereof are used, and as the lubricant, polyethylene glycol and the like are used. As the stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, are used.

A nucleus can also be prepared by, in addition to the above-mentioned, for example, a rolling granulation method in which a drug or a mixture of a drug with an excipient, lubricant and the like is added portionwise onto an inert carrier particle which is the core of the nucleus while spraying a binder dissolved in a suitable solvent such as water, lower alcohol (e.g., methanol, ethanol and the like) and the like, a pan coating method, a fluidized bed coating method or a melt granulating method. As the inert carrier particle, for example, those made of sucrose, lactose, starch, crystalline cellulose, waxes can be used, and the average particle size thereof is preferably from about 100 μm to about 1500 μm.

For separating a drug and a film agent contained in a nucleus, the surface of the nucleus may be coated with a protective agent. As the protective agent, for example, the above-mentioned hydrophilic substances, water-insoluble substances and the like are used. As the protective agent, preferably polyethylene glycol, and polysaccharides having a hydroxyalkyl group or carboxyalkyl group are used, more preferably, hydroxypropylmethylcellulose and hydroxypropylcellulose are used. The protective agent may contain, as a stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, and lubricants such as talc and the like. When the protective agent is used, the coating amount is from about 1 to about 15% (w/w), preferably from about 1 to about 10% (w/w), further preferably from about 2 to about 8% (w/w), based on the nucleus.

The protective agent can be coated by a usual coating method, and specifically, the protective agent can be spray coated on a nucleus by, for example, a fluidized bed coating method, pan coating method and the like.

II. Coating of nucleus with film agent

A nucleus obtained in the above-mentioned step I is coated with a film agent solution obtained by heat-solving the above-mentioned water-insoluble substance and pH-dependent swellable polymer, and a hydrophilic substance, or by dissolving or dispersing them in a solvent, to give a sustained release preparation.

As the method for coating a nucleus with a film agent solution, for example, a spray coating method and the like are mentioned.

The composition ratio of a water-insoluble substance, swellable polymer and hydrophilic substance in a film agent solution is appropriately selected so that the contents of these components in a coated film are the above-mentioned contents, respectively.

The coating amount of a film agent is from about 1 to about 90% (w/w), preferably from about 5 to about 50% (w/w), further preferably from about 5 to about 35% (w/w), based on a nucleus (not including coating amount of protective agent).

As the solvent in a film agent solution, water or an organic solvent can be used alone or in admixture thereof. In the case of use in admixture, the mixing ratio of water to an organic solvent (water/organic solvent: by weight) can be varied in the range from 1 to 100%, and preferably from 1 to about 30%. The organic solvent is not particularly restricted providing it dissolves a water-insoluble substance, and for example, lower alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol and the like, lower alkanone such as acetone and the like, acetonitrile, chloroform,

methylene chloride and the like are used. Among them, lower alcohols are preferable, and ethyl alcohol and isopropyl alcohol are particularly preferable. Water, and a mixture of water with an organic solvent are preferably used as a solvent for a film agent. In this case, if necessary, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like may also be added into a film agent solution for stabilizing the film agent solution.

An operation of coating by spray coating can be effected by a usual coating method, and specifically, it can be effected by spray-coating a film agent solution onto a nucleus by a fluidized bed coating method, pan coating method and the like. In this case, if necessary, talc, titanium oxide, magnesium stearate, calcium stearate, light anhydrous silicic acid and the like may also be added as a lubricant, and glycerin fatty acid ester, hardened castor oil, triethyl citrate, cetyl alcohol, stearyl alcohol and the like may also be added as a plasticizer.

After coating with a film agent, if necessary, an antistatic agent such as talc and the like may be mixed.

The quick release preparation may be liquid (e.g., solution, suspension, emulsion and the like) or solid (e.g., particle, pill, tablet and the like). As the quick release preparation, oral agents and parenteral agents such as an injection and the like are used, and oral agents are preferable.

The quick release preparation, usually, may contain, in addition to an active component drug, also carriers, additives and excipients conventionally used in the production field (hereinafter, sometimes abbreviated as excipient). The excipient used is not particularly restricted providing it is an excipient ordinarily used as a preparation excipient. For example, as the excipient for an oral solid preparation, lactose, starch, corn starch, crystalline cellulose (Avicel PH101, manufactured by Asahi Chemical Industry Co., Ltd., and

the like), powder sugar, granulated sugar, mannitol, light anhydrous silicic acid, magnesium carbonate, calcium carbonate, L-cysteine and the like are mentioned, and preferably, corn starch and mannitol and the like are mentioned. These excipients can be used alone or in combination of two or more. The content of the excipient is, for example, from about 4.5 to about 99.4% (w/w), preferably from about 20 to about 98.5% (w/w), further preferably from about 30 to about 97% (w/w), based on the total amount of the quick release preparation.

The content of a drug in the quick release preparation can be appropriately selected in the range from about 0.5 to about 95% (w/w), preferably from about 1 to about 60% (w/w) based on the total amount of the quick release preparation.

When the quick release preparation is an oral solid preparation, it usually contains, in addition to the above-mentioned components, also a disintegrant. As this disintegrant, there are used, for example, carboxymethylcellulose calcium (ECG-505, manufactured by Gotoku Yakuhin), crosscarmelose sodium (e.g., Ac-Di-Sol, manufactured by Asahi Chemical Industry Co., Ltd.), Crospovidone (e.g., Kollidon CL, manufactured by BASF), low-substituted hydroxypropylcellulose (manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethylstarch (manufactured by Matsutani Kagaku K.K.), carboxymethylstarch sodium (Exprotab, manufactured by Kimura Sangyo), partially pregelatinized starch (PCS, manufactured by Asahi Chemical Industry Co., Ltd.), and the like are used, and for example, those which disintegrate a granule by adsorbing water in contact with water, causing swelling, or making a channel between an effective ingredient constituting the nucleus and an excipient, can be used. These disintegrants can be used alone or in combination of two or more. The amount of the disintegraent used is appropriately selected depending on the kind and compounding amount of a drug used, design of releasing property, and the like, and for

example, from about 0.05 to about 30% (w/w), preferably from about 0.5 to about 15% (w/w), based on the total amount of the quick releasing agent.

When the quick release preparation is an oral solid preparation, it may further contain, in addition to the above-mentioned composition, if desired, additives conventional in solid preparations. As such an additive, there are used, for example, a binder (e.g., sucrose, gelatin, gum Arabic powder, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, pullulan, dextrin and the like), a lubricant (e.g., polyethylene glycol, magnesium stearate, talc, light anhydrous silicic acid (e.g., aerosil (Nippon Aerosil)), a surfactant (e.g., anionic surfactants such as sodium alkylsulfate and the like, nonionic surfactants such as polyoxyethylene fatty acid ester and polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil derivatives and the like), a coloring agent (e.g., tar pigment, caramel, iron oxide red, titanium oxide, riboflavins, and the like), if necessary, an appetizing agent (e.g., sweetening agent, aroma and the like), an adsorbing agent, preservative, wetting agent, antistatic agent, and the like. Further, as the stabilizer, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid and the like may also be added.

As the above-mentioned binder, hydroxypropylcellulose, polyethylene glycol and polyvinylpyrrolidone and the like are preferably used.

The quick releasing preparation can be prepared by, based on a usual technology of producing preparations, mixing the above-mentioned components, and if necessary, further kneading the mixture, and molding it. The above-mentioned mixing is conducted by generally used methods, for example, mixing, kneading and the like. Specifically, when a quick release preparation is formed, for example, into a particle, it can be

prepared, according to the same methods as in the above-mentioned method for preparing a nucleus of a sustained release preparation, by mixing the components using a vertical granulator, universal kneader (manufactured by Hata Tekkosho), fluidized bed granulator FD-5S (manufactured by Powrex), and the like, then, subjecting the mixture to a wet extrusion granulation method, fluidized bed granulation method and the like.

Thus obtained quick releasing preparation and sustained releasing preparation may be themselves made into products or made into products appropriately together with preparation excipients and the like, separately, by an ordinary method, then, may be administered simultaneously or may be administered in combination at any administration interval, or they may be themselves made into one oral preparation (e.g., granule, fine particle, tablet, capsule and the like) or made into one oral preparation together with preparation excipients and the like. It may also be permissible that they are made into granules or fine particles, and filled in the same capsule to be used as a preparation for oral administration.

[3] Sublingual, buccal or intraoral quick disintegrating agent and preparation thereof

Sublingual, buccal or intraoral quick disintegrating agents may be a solid preparation such as tablet and the like, or may be an oral mucosa membrane patch (film).

As the sublingual, buccal or intraoral quick disintegrating agent, a preparation containing the compound of the present invention or the concomitant drug and an excipient is preferable. It may contain also auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer and the like. Further, for easy absorption and increase in *in vivo* use efficiency, β-cyclodextrin or β-cyclodextrin derivatives (e.g., hydroxypropyl-β-cyclodextrin and the like) and the like may

also be contained.

As the above-mentioned excipient, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like are mentioned. As the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica and the like are mentioned, and particularly, magnesium stearate and colloidal silica are preferable. As the isotonizing agent, sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin, urea and the like are mentioned, and particularly, mannitol is preferable. As the hydrophilic carrier, swellable hydrophilic carriers such as crystalline cellulose, ethylcellulose, crosslinkable polyvinylpyrrolidone, light anhydrous silicic acid, silicic acid, dicalcium phosphate, calcium carbonate and the like are mentioned, and particularly, crystalline cellulose (e.g., fine crystalline cellulose and the like) is preferable. As the water-dispersible polymer, gums (e.g., gum tragacanth, acacia gum, cyamoposis gum), alginates (e.g., sodium alginate), cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose), gelatin, water-soluble starch, polyacrylic acids (e.g., Carbomer), polymethacrylic acid, polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, polycarbofil, ascorbate palmitates and the like are mentioned, and hydroxypropylmethylcellulose, polyacrylic acid, alginate, gelatin, carboxymethylcellulose, polyvinylpyrrolidone, polyethylene glycol and the like are preferable. Particularly, hydroxypropylmethylcellulose is preferable. As the stabilizer, cysteine, thiosorbitol, tartaric acid, citric acid, sodium carbonate, ascorbic acid, glycine, sodium sulfite and the like are mentioned, and particularly, citric acid and ascorbic acid are preferable.

The sublingual, buccal or intraoral quick disintegrating agent can be produced by mixing the compound of the present

invention or the concomitant drug and an excipient by a method known *per se*. Further, if desirable, auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer, coloring agent, sweetening agent, preservative and the like may be mixed. The sublingual, buccal or intraoral quick disintegrating agent is obtained by mixing the above-mentioned components simultaneously or at a time interval, then subjecting the mixture to tablet-making molding under pressure. For obtaining suitable hardness, it may also be permissible that the materials are moistened by using a solvent such as water, alcohol and the like if desired before and after the tablet making process, and after the molding, the materials are dried, to obtain a product.

In the case of molding into a mucosa membrane patch (film), the compound of the present invention or the concomitant drug and the above-mentioned water-dispersible polymer (preferably, hydroxypropylcellulose, hydroxypropylmethylcellulose), excipient and the like are dissolved in a solvent such as water and the like, and the resulted solution is cast, to give a film. Further, additives such as a plasticizer, stabilizer, antioxidant, preservative, coloring agent, buffer, sweetening agent and the like may also be added. For imparting suitable elasticity to the film, glycols such as polyethylene glycol, propylene glycol and the like may be contained, or for enhancing adhesion of the film to an intraoral mucosa membrane lining, a bio-adhesive polymer (e.g., polycarbofil, carbopol) may also be contained. In the casting, a solution is poured on the non-adhesive surface, spread to uniform thickness (preferably 10 to 1000 micron) by an application tool such as a doctor blade and the like, then, the solution is dried to form a film. It may be advantageous that thus formed film is dried at room temperature or under heat, and cut into given area.

As the preferable intraoral quick disintegrating agent, there are mentioned solid quick scattering dose agents composed

of a network body comprising the compound of the present invention or the concomitant drug, and a water-soluble or water-diffusible carrier which is inert to the compound of the present invention or concomitant drug, are mentioned. This network body is obtained by sublimating a solvent from the solid composition constituted of a solution prepared by dissolving the compound of the present invention or the concomitant drug in a suitable solvent.

It is preferable that the composition of an intraoral quick disintegrating agent contains a matrix forming agent and a secondary component, in addition to the compound of the present invention or the concomitant drug.

Examples of the matrix forming agent include animal proteins or vegetable proteins such as gelatins, dextrins and, soybean, wheat and psyllium seed protein and the like; rubber substances such as gum Arabic, cyamoposis gum, agar, xanthan gum and the like; polysaccharides; alginic acids; carboxymethylcelluloses; carageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone and the like; substances derived from a gelatin-gum Arabic complex, and the like. Further, saccharides such as mannitol, dextrose, lactose, galactose, trehalose and the like; cyclic saccharides such as cyclodextrin and the like; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicate and the like; amino acid s having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine and the like, are contained.

One or more of the matrix forming agents can be introduced in a solution or suspension before solidification. Such matrix forming agent may be present in addition to a surfactant, or may be present while a surfactant being excluded. The matrix forming agent aids to maintain the compound of the present invention or the concomitant drug in the solution or suspension

in diffused condition, in addition to formation of the matrix.

The composition may contain secondary components such as preservative, antioxidant, surfactant, thickening agent, coloring agent, pH regulator, flavoring agent, sweetening agent, food taste masking agent and the like. As the suitable coloring agent, red, black and yellow iron oxides, and FD & C dyes such as FD & C Blue 2, FD & C Red 40 and the like manufactured by Elis and Eberald can be mentioned. Examples of suitable flavoring agents include mint, raspberry, licorice, orange, lemon, grape fruit, caramel, vanilla, cherry, grape flavor and combinations thereof. Examples of suitable pH regulators include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of suitable sweetening agents include aspartame, acesulfame K and thaumatin and the like. Examples of suitable food taste masking agents include sodium bicarbonate, ion exchange resin, cyclodextrin-containing compounds, adsorbent substances and microcapsulated apomorphine.

The preparation contains the compound of the present invention or a concomitant drug in an amount generally from about 0.1 to about 50% by weight, preferably from about 0.1 to about 30% by weight, and preferred are preparations (such as the above-mentioned sublingual agent, buccal and the like) which can dissolve 90% or more of the compound of the present invention or the concomitant drug (into water) within the time range of about 1 to about 60 minutes, preferably about 1 to about 15 minutes, more preferably about 2 to about 5 minutes, and intraoral quick disintegrating preparations which are disintegrated within the range of 1 to 60 seconds, preferably 1 to 30 seconds, further preferably 1 to 10 seconds, after placement in an oral cavity.

The content of the above-mentioned excipient in the whole preparation is from about 10 to about 99% by weight, preferably from about 30 to about 90% by weight. The content of β-

cyclodextrin or β-cyclodextrin derivative in the whole preparation is from 0 to about 30% by weight. The content of the lubricant in the whole preparation is from about 0.01 to about 10% by weight, preferably from about 1 to about 5% by weight. The content of the isotonizing agent in the whole preparation is from about 0.1 to about 90% by weight, preferably, from about 10 to about 70% by weight. The content of the hydrophilic carrier agent in the whole preparation is from about 0.1 to about 50% by weight, preferably, from about 10 to about 30% by weight. The content of the water-dispersible polymer in the whole preparation is from about 0.1 to about 30% by weight, preferably, from about 10 to about 25% by weight. The content of the stabilizer in the whole preparation is from about 0.1 to about 10% by weight, preferably, from about 1 to about 5% by weight. The above-mentioned preparation may further contain additives such as a coloring agent, sweetening agent, preservative and the like, if necessary.

The dosage of a concomitant agent of the present invention differs depending on the kind of the compound of the present invention, age, body weight, condition, preparation form, administration method, administration period and the like, and for example, for one diabetic patient (adult, body weight: about 60 kg), the concomitant agent is administered intravenously, at a dose of about 0.01 to about 1000 mg/kg/day, preferably about 0.01 to about 100 mg/kg/day, more preferably about 0.1 to about 100 mg/kg/day, particularly about 0.1 to about 50 mg/kg/day, especially about 1.5 to about 30 mg/kg/day, in terms of the compound of the present invention or the concomitant drug, respectively, once or divided several times in a day. Of course, since the dosage as described above varies depending on various conditions, amounts smaller than the above-mentioned dosage may sometimes be sufficient, further, amounts over that range sometimes have to be administered.

The amount of the concomitant drug can be set at any value unless side effects are problematical. The daily dosage in terms of the concomitant drug differs depending on the severity, age, sex, body weight, sensitivity difference of the subject, administration period, interval, and nature, pharmacology, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, usually from about 0.001 to 2000 mg, preferably from about 0.01 to 500 mg, further preferably from about 0.1 to 100 mg, per 1 kg of a mammal and this is usually administered once to 4-times divided in a day.

For administration of a concomitant agent of the present invention, the compound of the present invention may be administered after administration of the concomitant drug or the concomitant drug may be administered after administration of the compound of the present invention, though they may be administered simultaneously. When administered at a time interval, the interval varies depending on the effective ingredient, preparation form and administration method, and, for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 minute to 3 days, preferably from 10 minutes to 1 day, more preferably from 15 minutes to 1 hour, after administration of the concomitant drug is exemplified. When the compound of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 minute to 1 day, preferably from 10 minutes to 6 hours, more preferably from 15 minutes to 1 hour after administration of the compound of the present invention is exemplified.

In a preferable administration method, for example, the concomitant drug which has been formed into an oral administration preparation is administered orally at a daily

dose of about 0.001 to 200 mg/kg, and about 15 minutes after, the compound of the present invention which has been formed into an oral administration preparation is administered orally at a daily dose of about 0.005 to 100 mg/kg.

【Embodiments of the Invention】

The present invention is explained in detail in the following by referring to Reference Examples, Examples, Formulation Examples and Experimental Examples, which are mere embodiments and do not limit the present invention. They may be modified within the range that does not deviate from the scope of the present invention.

In the following Reference Examples and Examples, the "room temperature" generally means about 10°C to about 35°C. As to %, yield means mol/mol%, the solvent used for chromatography means % by volume, and others mean wt%. Those that cannot be confirmed by proton NMR spectrum, such as OH and NH protons that are broad, are not described in the data.

Other abbreviations used in the specification mean the following.

s : singlet
d : doublet
t : triplet
q : quartet
m : multiplet
br : broad
J : coupling constant
Hz : Hertz
$CDCl_3$: deuterated chloroform
DMSO-d_6: deuterated dimethyl sulfoxide
^1H NMR : proton nuclear magnetic resonance

【Examples】

Reference Example 1 methyl 4-(phenylmethoxy)benzenepropanoate

To an ice-cooled solution of methyl 4-hydroxybenzenepropanoate (0.70 g, 3.9 mmol), benzyl alcohol

(0.48 mL, 4.7 mmol) and triphenylphosphine (1.2 g, 4.7 mmol) in tetrahydrofuran (5 mL) was added dropwise diethyl azodicarboxylate (0.73 mL, 4.7 mmol), and the mixture was stirred under ice-cooling for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=17:3) to give the title compound (0.62 g, yield 59%) as a powder.

^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J=7.5 Hz), 2.89 (2H, t, J=7.5 Hz), 3.66 (3H, s), 5.04 (2H, s), 6.90 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz), 7.29-7.44 (5H, m).

Reference Example 2 4-(phenylmethoxy)benzenepropanoic acid

To a suspension of methyl 4-(phenylmethoxy)benzenepropanoate (0.60 g, 2.2 mmol) in methanol (20 mL) was added 2N aqueous sodium hydroxide solution (2 mL), and the mixture was stirred at 60°C for 15 hrs. 2N Hydrochloric acid (3 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give the title compound (0.38 g, yield 67%).

melting point: 123-124°C.

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.5 Hz), 2.90 (2H, t, J=7.5 Hz), 5.04 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz), 7.28-7.44 (5H, m).

Reference Example 3 methyl 4-(2-phenylethoxy)benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and phenethyl alcohol by a method similar to that of Reference Example 1. yield 89%, oil.

^{1}H NMR ($CDCl_3$) δ 2.58 (2H, t, J=7.5 Hz), 2.88 (2H, t, J=7.5 Hz), 3.08 (2H, t, J=7.1 Hz), 4.14 (2H, t, J=7.1 Hz), 6.81 (2H, d, J=8.6 Hz), 7.09 (2H, d, J=8.6 Hz), 7.20-7.34 (5H, m).

Reference Example 4 4-(2-phenylethoxy)benzenepropanoic acid

To a solution of methyl 4-(2-phenylethoxy)benzenepropanoate (0.65 g, 2.3 mmol) in methanol (3 mL) was added 2N aqueous sodium hydroxide solution (3 mL), and the mixture was stirred at 50°C for 1 hr. 2N Hydrochloric acid (2.5 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give the title compound (0.50 g, yield 81%).

melting point: 91-92°C.

^{1}H NMR ($CDCl_3$) δ 2.63 (2H, t, J=7.5 Hz), 2.89 (2H, t, J=7.5 Hz), 3.08 (2H, t, J=7.2 Hz), 4.15 (2H, t, J=7.2 Hz), 6.82 (2H, d, J=8.6 Hz), 7.10 (2H, d, J=8.6 Hz), 7.20-7.34 (5H, m).

Reference Example 5 ethyl 4-(3-phenylpropoxy)benzenepropanoate

To an ice-cooled solution of ethyl 4-hydroxybenzenepropanoate (0.40 g, 2.1 mmol) in N,N-dimethylformamide (15 mL) was added 60% sodium hydride (0.11 g, 2.7 mmol), and the mixture was stirred for 30 min. 1-Bromo-3-phenylpropane (0.53 g, 2.7 mmol) was added, and the mixture was stirred at room temperature for 3 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=18:1) to give the title compound (0.29 g, yield 46%). oil.

^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J=7.1 Hz), 2.04-2.13 (2H, m), 2.58 (2H, t, J=8.1 Hz), 2.88 (2H, t, J=8.1 Hz), 3.94 (2H, t, J=6.3 Hz), 4.12 (2H, q, J=7.1 Hz), 6.81 (2H, d, J=8.6 Hz), 7.10 (2H, d, J=8.6 Hz), 7.19-7.31 (5H, m).

Reference Example 6 4-(3-phenylpropoxy)benzenepropanoic acid

The title compound was obtained from ethyl 4-(3-phenylpropoxy)benzenepropanoate by a method similar to that of Reference Example 4. yield 45%.

melting point: 109-110°C (recrystallized from diethyl ether-

hexane).

^{1}H NMR ($CDCl_3$) δ2.05-2.13 (2H, m), 2.65 (2H, t, J=7.8 Hz), 2.80 (2H, t, J=7.8 Hz), 2.90 (2H, t, J=7.9 Hz), 3.94 (2H, t, J=6.3 Hz), 6.82 (2H, d, J=8.5 Hz), 7.11 (2H, d, J=8.5 Hz), 7.16-7.31 (5H, m).

Reference Example 7 ethyl 4-(4-phenylbutoxy)benzenepropanoate

The title compound was obtained from ethyl 4-hydroxybenzenepropanoate by a method similar to that of Reference Example 5. yield 55%, oil.

^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J=7.1 Hz), 1.76-1.85 (4H, m), 2.57 (2H, t, J=7.4 Hz), 2.66-2.70 (2H, m), 2.88 (2H, t, J=8.1 Hz), 3.92-3.96 (2H, m), 4.12 (2H, q, J=7.1 Hz), 6.79-6.82 (m, 2H), 7.08-7.11 (m, 2H), 7.18-7.20 (m, 3H), 7.26-7.30 (m, 2H).

Reference Example 8 4-(4-phenylbutoxy)benzenepropanoic acid

The title compound was obtained from ethyl 4-(4-phenylbutoxy)benzenepropanoate by a method similar to that of Reference Example 4. yield 61%.

melting point: 79.5-80.0°C (recrystallized from diethyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 1.70-1.90 (4H, m), 2.61-2.70 (4H, m), 2.89 (2H, t, J=7.9 Hz), 3.92-3.96 (2H, m), 6.81 (2H, d, J=8.6 Hz), 7.06 (2H, d, J=8.6 Hz), 7.12-7.31 (m, 5H).

Reference Example 9 ethyl 4-[(4-phenoxybenzoyl)amino]benzenepropanoate

To a solution of ethyl 4-aminobenzenepropanoate (0.70 g, 3.6 mmol) in N,N-dimethylformamide (25 mL) were added 4-phenoxybenzoic acid (0.85 g, 4.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.76 g, 4.0 mmol) and 1-hydroxybenzotriazole monohydrate (0.61 g, 4.0 mmol), and the mixture was stirred at room temperature for 16 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=2:1) to

give the title compound (0.96 g, yield 68%) as a white powder. ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J=7.1 Hz), 2.61 (2H, t, J=8.0 Hz), 2.94 (2H, t, J=7.9 Hz), 4.13 (2H, q, J=7.1 Hz), 7.03-7.08 (4H, m), 7.16-7.21 (3H, m), 7.36-7.43 (2H, m), 7.54 (2H, t, J=8.5 Hz), 7.73 (1H,s), 7.84 (2H, d, J=8.7 Hz).

Reference Example 10 4-[(4-phenoxybenzoyl)amino]benzenepropanoic acid

The title compound was obtained from ethyl 4-[(4-phenoxybenzoyl)amino]benzenepropanoate by a method similar to that of Reference Example 4. yield 76%.

melting point: 214-215°C (recrystallized from tetrahydrofuran-hexane).

^{1}H NMR (DMSO-d_6) δ 2.52 (2H, t, J=7.6 Hz), 2.79 (2H, t, J=7.6 Hz), 7.07-7.12 (4H, m), 7.18-7.25 (3H, m), 7.45 (2H, t, J=7.4 Hz), 7.65 (2H, d, J=8.4 Hz), 7.98 (2H, d, J=8.7 Hz), 10.11 (1H, s).

Reference Example 11 ethyl 4-[3-[methyl(4-phenyl-2-thiazolyl)amino]propoxy]benzenepropanoate

To an ice-cooled solution of N-methyl-4-phenyl-2-thiazolamine (0.30 g, 1.7 mmol) in N,N-dimethylformamide (5 mL) was added 60% sodium hydride (72 mg, 1.8 mmol), and the mixture was stirred for 30 min. Ethyl 4-[(3-bromopropyl)oxy]benzenepropanoate (0.57 g, 1.8 mmol), was added, and the mixture was stirred at room temperature for 3 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=15:1) to give the title compound (0.58 g, yield 80%). oil.

^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J=7.1 Hz), 2.10-2.30 (2H, m), 2.58 (2H, t, J=6.8 Hz), 2.88 (2H, t, J=6.8 Hz), 3.14 (3H, s), 3.73 (2H, t, J=6.8 Hz), 4.03 (2H, t, J=6.0 Hz), 4.12 (2H, q, J=7.1 Hz), 6.70 (1H, d, J=3.8 Hz), 6.83 (2H, d, J=8.6 Hz), 7.10 (2H, d, J=8.6 Hz), 7.20-7.30 (1H, m), 7.30-7.38 (2H, m),

7.82-7.85 (2H, m).

Reference Example 12 4-[3-[methyl(4-phenyl-2-thiazolyl)amino]propoxy]benzenepropanoic acid

The title compound was obtained from ethyl 4-[3-[methyl(4-phenyl-2-thiazolyl)amino]propoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 13%.
melting point: 89-90°C (recrystallized from diethyl ether-hexane).
^{1}H NMR ($CDCl_3$) δ 2.14-2.23 (2H, m), 2.64 (2H, t, J=7.9 Hz), 2.90 (2H, t, J=7.9 Hz), 3.14 (3H, s), 3.73 (2H, d, J=6.8 Hz), 4.03 (2H, t, J=6.0 Hz), 6.69 (1H, s), 6.84 (2H, d, J=8.5 Hz), 7.11 (2H, d, J=8.5 Hz), 7.23-7.33 (1H, m), 7.35 (2H, t, J=7.7 Hz), 7.82 (2H, d, J=7.2 Hz).

Reference Example 13 1-[(4-bromo-2,6-difluorophenyl)oxy]-2,3-dihydro-1H-indene

The title compound was obtained from 1-indanol and 4-bromo-2,6-difluorophenol by a method similar to that of Reference Example 1. yield 74%.
melting point: 46-46°C (recrystallized from ethyl acetate).
^{1}H NMR ($CDCl_3$) δ 2.34-2.40 (2H, m), 2.83-2.92 (1H, m), 3.20-3.31 (1H, m), 5.64 (1H, t, J=4.4 Hz), 7.04-7.13 (2H, m), 7.17-7.22 (1H, m), 7.28-7.32 (3H, m).

Reference Example 14 ethyl 4-[[4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzoyl]amino]benzenepropanoate

The title compound was obtained as a white powder from ethyl 3-(4-aminophenyl)propionate and 4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzoic acid by a method similar to that of Reference Example 9. yield 89%.
^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J=7.1 Hz), 2.61 (2H, t, J=7.9 Hz), 2.94 (2H, t, J=7.9 Hz), 3.10 (3H, s), 4.12 (2H, q, J=7.1 Hz), 4.86 (2H, s), 6.75 (1H, s), 7.20 (2H, d, J=8.4 Hz), 7.26-7.30 (2H, m), 7.38 (2H, t, J=7.8 Hz), 7.46 (2H, d, J=8.2 Hz), 7.54 (2H, d, J=8.4 Hz), 7.75 (1H, s), 7.82-7.87 (3H, m).

Reference Example 15 4-[[4-[[methyl(4-phenyl-2-

thiazolyl)amino]methyl]benzoyl]amino]benzenepropanoic acid

The title compound was obtained from ethyl 4-[[4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzoyl]amino]benzenepropanoate by a method similar to that of Reference Example 4. yield 79%. melting point: 183-184°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J=7.5 Hz), 2.94 (2H, t, J=7.5 Hz), 3.08 (3H, s), 4.84 (2H, s), 6.75 (1H, s), 7.20 (2H, d, J=8.5 Hz), 7.22-7.30 (1H, m), 7.30-7.44 (4H, m), 7.55 (2H, d, J=8.4 Hz), 7.80-7.87 (5H, m).

Reference Example 16 methyl (E)-3-[4-[(2,3-dihydro-1H-inden-1-yl)oxy]-3,5-difluorophenyl]-2-propenoate

The title compound was obtained from 1-[(4-bromo-2,6-difluorophenyl)oxy]-2,3-dihydro-1H-indene by a method similar to that of Reference Example 34. yield 40%.
melting point: 74-75°C (recrystallized from ethyl acetate-diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ 2.37-2.43 (2H, m), 2.84-2.93 (1H, m), 2.32-3.32 (1H, m), 3.81 (3H, s), 5.74 (1H, t, J=4.5 Hz), 6.34 (1H, d, J=16 Hz), 7.03-7.12 (2H, m), 7.16-7.23 (1H, m), 7.28-7.35 (2H, m), 7.53 (1H, d, J=16 Hz).

Reference Example 17 methyl 4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzeneacetate

The title compound was obtained from methyl 4-hydroxybenzeneacetate and 2,3-dihydro-1H-inden-1-ol by a method similar to that of Reference Example 1. yield 69%, oil.

^{1}H NMR ($CDCl_3$) δ 2.10-2.30 (1H, m), 2.45-2.65 (1H, m), 2.52-2.57 (1H, m), 3.09-3.19 (1H, m), 3.59 (2H, s), 3.70 (3H, s), 5.75 (1H, dd, J=6.6 Hz, 4.4 Hz), 6.95-6.98 (2H, m), 7.21-7.32 (5H, m), 7.43 (1H, d, J=7.2 Hz).

Reference Example 18 methyl 4-[(4-nitrophenyl)methoxy]benzenepropanoate

The title compound was obtained as a yellow powder from

methyl 4-hydroxybenzenepropanoate and 4-nitrobenzylbromide by a method similar to that of Reference Example 5. yield 41%.
^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.66 (3H, s), 5.15 (2H, s), 6.88 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.60 (2H, d, J=8.7 Hz), 8.23-8.28 (2H, m).

Reference Example 19 4-[(4-nitrophenyl)methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(4-nitrophenyl)methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 26%.
melting point: 179-181°C (recrystallized from ethyl acetate-hexane).
^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.7 Hz), 2.91 (2H, t, J=7.7 Hz), 5.15 (2H, s), 6.89 (2H, d, J=8.5 Hz), 7.15 (2H, d, J=8.5 Hz), 7.60 (2H, d, J=8.5 Hz), 8.24 (2H, d, J=8.6 Hz).

Reference Example 20 4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzeneacetic acid

The title compound was obtained from methyl 4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzeneacetate by a method similar to that of Reference Example 4. yield 52%.
melting point: 121.0-121.5°C (recrystallized from ethyl acetate-hexane).
^{1}H NMR ($CDCl_3$) δ 2.10-2.26 (1H, m), 2.45-2.60 (1H, m), 2.80-2.97 (1H, m), 3.09-3.14 (1H, m), 3.61 (2H, s), 5.74 (1H, dd, J=6.7 Hz, 4.4 Hz), 6.97 (2H, d, J=8.6 Hz), 6.99-7.34 (5H, m), 7.42 (1H, d, J=7.2 Hz).

Reference Example 21 4-(4-phenoxyphenoxy)benzaldehyde

To a solution of 4-phenoxyphenol (1.0 g, 5.4 mmol) in N,N-dimethylformamide (20 mL) were added 4-fluorobenzaldehyde (0.67 g, 5.4 mmol) and potassium carbonate (0.75 g, 5.4 mmol), and the mixture was stirred at 100°C for 15 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel

column chromatography (hexane/ethyl acetate=9:1) to give the title compound (1.4 g, yield 89%).

^{1}H NMR ($CDCl_3$) δ 7.02-7.12 (9H, m), 7.36 (2H, dd, J=7.5 Hz, 8.5 Hz), 7.85 (2H, d, J=8.7 Hz), 9.92 (1H, s).

Reference Example 22 4-([1,1'-biphenyl]-4-yloxy)benzaldehyde

The title compound was obtained from 4-hydroxybiphenyl and 4-fluorobenzaldehyde by a method similar to that of Reference Example 21. yield 37%.

^{1}H NMR ($CDCl_3$) δ 7.10-7.19 (4H, m), 7.35-7.49 (3H, m), 7.58-7.66 (4H, m), 7.87 (2H, d, J=8.7 Hz), 9.94 (1H, s).

Reference Example 23 4-[4-(phenylmethoxy)phenoxy]benzaldehyde

The title compound was obtained from 4-benzyloxyphenol and 4-fluorobenzaldehyde by a method similar to that of Reference Example 21. yield 57%.

^{1}H NMR ($CDCl_3$) δ 5.08 (2H, s), 7.00-7.03 (6H, m), 7.34-7.46 (5H, m), 7.83 (2H, d, J=8.7 Hz), 9.91 (1H, s).

Reference Example 24 4-(4-phenoxyphenoxy)benzyl alcohol

The title compound was obtained from 4-(4-phenoxyphenoxy)benzaldehyde by a method similar to that of Reference Example 32. yield 82%.

^{1}H NMR ($CDCl_3$) δ 1.64 (1H, s), 4.66 (2H, s), 6.98-7.01 (8H, m), 7.09 (1H, t, J=7.3 Hz), 7.31-7.36 (4H, m).

Reference Example 25 4-([1,1'-biphenyl]-4-yloxy)benzyl alcohol

The title compound was obtained from 4-([1,1'-biphenyl]-4-yloxy)benzaldehyde by a method similar to that of Reference Example 32. yield 66%.

^{1}H NMR ($CDCl_3$) δ 1.64 (1H, s), 4.69 (2H, s), 7.03-7.08 (4H, m), 7.35-7.48 (5H, m), 7.54-7.58 (4H, m).

Reference Example 26 4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzaldehyde

To a solution of 4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzenemethanol (1.0 g, 3.2 mmol) in ethyl acetate (40 mL) was added manganese dioxide (4.0 g), and the mixture was stirred at room temperature for 3 hrs.

Insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=5:1) to give the title compound (0.80 g, yield 81%). oil.

^{1}H NMR ($CDCl_3$) δ 3.10 (3H, s), 4.88 (2H, s), 6.75 (1H, s), 7.25-7.30 (1H, m), 7.35-7.40 (2H, m), 7.51 (2H, d, J=8.0 Hz), 7.83-7.88 (4H, m), 10.00 (1H, s).

Reference Example 27 ethyl (E)-3-[4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]phenyl]propenoate

To an ice-cooled solution of ethyl diethylphosphonoacetate (0.81 g, 3.6 mmol) in tetrahydrofuran (10 mL) was added 60% sodium hydride (0.14 g, 3.4 mmol), and the mixture was stirred for 30 min. A solution of 4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzaldehyde (0.80 g, 2.6 mmol) in tetrahydrofuran (10 mL) was added dropwise. The mixture was stirred at room temperature for 3 hrs, water was added, and the mixture was extracted with ethyl acetate. The extract was dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=18:1) to give the title compound (0.96 g, yield 98%) as a powder.

^{1}H NMR ($CDCl_3$) δ 1.33 (3H, t, J=7.1 Hz), 3.08 (3H, s), 4.26 (2H, q, J=7.1 Hz), 4.80 (2H, s), 6.42 (1H, d, J=16.0 Hz), 6.74 (1H, s), 7.25-7.39 (5H, m), 7.50 (2H, d, J=8.2 Hz), 7.67 (1H, d, J=16.0 Hz), 7.86 (2H, d, J=7.2 Hz).

Reference Example 28 ethyl 4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzenepropanoate

To a solution of ethyl (E)-3-[4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]phenyl]propenoate (0.60 g, 1.6 mmol) and nickel chloride hexahydrate (0.41 g, 3.2 mmol) in ethanol (25 mL) was added sodium borohydride (0.30 g, 8.0 mmol), and the mixture was stirred at room temperature for 2 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with

water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=18:1) to give the title compound (0.39 g, yield 64%). oil.
^1H NMR ($CDCl_3$) δ 1.23 (3H, t, J=7.1 Hz), 2.60 (2H, t, J=8.0 Hz), 2.94 (2H, t, J=8.0 Hz), 3.06 (3H, s), 4.12 (2H, q, J=7.1 Hz), 4.73 (2H, s), 6.72 (1H, s), 7.17 (2H, d, J=8.0 Hz), 7.25-7.30 (3H, m), 7.35-7.40 (2H, m), 7.85-7.88 (2H, m).

Reference Example 29 4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzenepropanoic acid

The title compound was obtained from ethyl 4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]benzenepropanoate by a method similar to that of Reference Example 4. yield 64%.
melting point: 109-110°C (recrystallized from ethyl acetate-hexane).
^1H NMR ($CDCl_3$) δ 2.66 (2H, t, J=7.9 Hz), 2.94 (2H, t, J=7.9 Hz), 3.06 (3H, s), 4.73 (2H, s), 6.71 (1H, s), 7.17 (2H, d, J=8.0 Hz), 7.25-7.34 (3H, m), 7.37 (2H, t, J=7.8 Hz), 7.86 (2H, d, J=7.2 Hz).

Reference Example 30 4-[4-(phenylmethoxy)phenoxy]benzyl alcohol

The title compound was obtained from 4-[4-(phenylmethoxy)phenoxy]benzaldehyde by a method similar to that of Reference Example 32. yield 88%.
^1H NMR ($CDCl_3$) δ 1.60(1H, s), 4.65 (2H, s), 5.05 (2H, s), 6.92-6.96 (6H, m), 7.29-7.45 (7H, m).

Reference Example 31 2,3-dihydro-5-(phenylmethoxy)-1H-inden-1-one

To a solution of 5-hydroxyindanone (1.0 g, 6.2 mmol), benzyl alcohol (0.65 g, 5.6 mmol) and tributylphosphine (1.7 g, 8.4 mmol) in tetrahydrofuran (30 mL) was added 1,1'-(azodicarbonyl)dipiperidine (2.1 g, 8.4 mmol), and the mixture was stirred at room temperature for 16 hrs. Insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography

(hexane/ethyl acetate=10:1) to give the title compound (1.3 g, yield 97%) as a powder.

^{1}H NMR ($CDCl_3$) δ 2.67(2H, t, J=6.1 Hz), 3.08 (2H, t, J=6.1 Hz), 5.15 (2H, s), 6.97 (2H, s), 7.30-7.45 (5H, m), 7.70 (1H, d, J=9.1 Hz).

Reference Example 32 2,3-dihydro-5-(phenylmethoxy)-1H-inden-1-ol

2,3-Dihydro-5-(phenylmethoxy)-1H-inden-1-one (1.3 g, 5.46 mmol) was dissolved in a mixture of tetrahydrofuran (20 mL) and methanol (10 mL), sodium borohydride (0.41 g, 11 mmol) was added, and the mixture was stirred at room temperature for 2 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=3:1) to give the title compound (1.16 g, yield 89%) as a white powder.

^{1}H NMR ($CDCl_3$) δ 1.70 (1H, d, J=5.0 Hz), 1.85-2.05 (1H, m), 2.40-2.55 (1H, m), 2.70-2.85 (1H, m), 2.95-3.10 (1H, m), 5.05 (2H, s), 5.10-5.20 (1H, m), 6.85-6.87 (1H, m), 7.25-7.45 (6H, m).

Reference Example 33 2-(4-bromophenoxy)-2,3-dihydro-1H-indene

The title compound was obtained from 2-indanol and 4-bromophenol by a method similar to that of Reference Example 1. yield 59%.

melting point: 83-84°C (recrystallized from ethyl acetate–diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ 3.13 (1H, d, J=3.0 Hz), 3.18 (1H, d, J=3.0 Hz), 3.33 (1H, d, J=6.2 Hz), 3.39 (1H, d, J=6.2 Hz), 5.09-5.15 (1H, m), 6.78 (2H, d, J=9.0 Hz), 7.16-7.26 (4H, m), 7.37 (2H, d, J=9.0 Hz).

Reference Example 34 methyl (E)-3-[4-[(2,3-dihydro-1H-inden-2-yl)oxy]phenyl]-2-propenoate

To a solution of 2-(4-bromophenoxy)-2,3-dihydro-1H-indene

(1.4 g, 4.7 mmol) in N,N-dimethylformamide (4.7 mL) were added sodium hydrogencarbonate (1.0 g, 12 mmol), methyl acrylate (0.86 mL, 9.5 mmol), tetrabutylammonium chloride (2.0 g, 7.1 mmol) and palladium acetate (31 mg, 0.14 mmol), and the mixture was stirred at 100°C for 24 hrs. The reaction mixture was allowed to return to room temperature and filtered. Water was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from ethyl acetate-hexane to give the title compound (0.96 g, yield 69%).

melting point: 115-116°C.

^{1}H NMR ($CDCl_3$) δ 3.16 (1H, d, J=2.9 Hz), 3.21 (1H, d, J=2.9 Hz), 3.37 (1H, d, J=6.4 Hz), 3.43 (1H, d, J=6.4 Hz), 3.80 (3H, s), 5.17-5.23 (1H, m), 6.31 (1H, d, J=16 Hz), 6.91 (2H, d, J=9.0 Hz), 7.17-7.27 (4H, m), 7.47 (2H, d, J=9.0 Hz), 7.65 (1H, d, J=16 Hz).

Reference Example 35 ethyl (4-methoxyphenoxy)acetate

To a solution of 4-methoxyphenol (5.0 g, 40 mmol) in N,N-dimethylformamide (50 mL) was added 60% sodium hydride (1.6 g, 40 mmol) under ice-cooling, and the mixture was stirred for 30 min. Ethyl bromoacetate (7.4 g, 44 mmol) was added thererto, and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=7:1) to give the title compound (8.0 g, yield 94%).

oil.

^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t, J=7.1 Hz), 3.77 (3H, s), 4.26 (2H, q, J=7.1 Hz), 4.57 (2H, s), 6.81-6.89 (4H, m).

Reference Example 36 ethyl (4-hydroxyphenoxy)acetate

A solution of ethyl (4-methoxyphenoxy)acetate (2.0 g, 9.5 mmol), ethanethiol (2.8 mL, 38 mmol) and aluminum chloride

(5.1 g, 38 mmol) in dichloromethane (20 mL) was stirred under ice-cooling for 40 min.. The reaction mixture was poured into a mixture of chloroform and saturated aqueous sodium hydrogencarbonate, and filtered through celite. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropyl ether to give the title compound (1.4 g, yield 75%).

melting point: 123-124°C.

^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t, J=7.1 Hz), 4.26 (2H, q, J=7.1 Hz), 4.56 (2H, s), 6.73-6.84 (4H, m).

Reference Example 37 ethyl [4-(4-phenylbutoxy)phenoxy]acetate

A solution of ethyl (4-hydroxyphenoxy)acetate (0.49 g, 2.5 mmol), 4-phenylbutyl bromide (0.59 g, 2.8 mmol), potassium carbonate (0.69 g, 5.0 mmol) and potassium iodide (30 mg, 0.50 mmol) in N,N-dimethylformamide (5 mL) was stirred at room temperature for 30 min., and further at 50°C for 3 hrs. The solvent was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and saturated brine. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=4:1) to give the title compound (0.62 g, yield 76%). oil.

^{1}H NMR ($CDCl_3$) δ 1.30 (3H, t, J=7.1 Hz), 1.78-1.83 (4H, m), 2.66-2.71 (2H, m), 3.90-3.94 (2H, m), 4.26 (2H, q, J=7.1 Hz), 4.56 (2H, s), 6.79-6.87 (4H, m), 7.18-7.21 (3H, m), 7.27-7.31 (2H, m).

Reference Example 38 [4-(4-phenylbutoxy)phenoxy]acetic acid

A mixture of ethyl [4-(4-phenylbutoxy)phenoxy]acetate (0.59 g, 1.8 mmol), lithium hydroxide monohydrate (0.15 g, 3.6 mmol), tetrahydrofuran (5 mL), methanol (1 mL) and water (3 mL) was stirred at room temperature for 48 hrs. The mixture was acidified with 1N hydrochloric acid, and extracted with

ethyl acetate. The extract was washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to give the title compound (0.48 g, yield 89%).

melting point: 116-117°C.

^{1}H NMR ($CDCl_3$) δ 1.78-1.82 (4H, m), 2.66-2.71 (2H, m), 3.90-3.94 (2H, m), 4.62 (2H, s), 6.81-6.88 (4H, m), 7.16-7.21 (3H, m), 7.27-7.31 (2H, m).

Reference Example 39 ethyl [(4-methoxyphenyl)thio]acetate

To an ice-cooled mixture of 4-methoxythiophenol (15 g, 0.11 mol), triethylamine (28 mL, 0.20 mol) and tetrahydrofuran (150 mL) was added ethyl bromoacetate (21 g, 0.13 mol), and the mixture was stirred overnight at room temperature. Ethanol (10 mL) was added, the solvent was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=10:1) to give title compound (22 g, yield 92%). oil.

^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J=7.1 Hz), 3.51 (2H, s), 3.79 (3H, s), 4.14 (2H, q, J=7.1 Hz), 6.83 (2H, d, J=8.8 Hz), 7.42 (2H, d, J=8.8 Hz).

Reference Example 40 ethyl [(4-hydroxyphenyl)thio]acetate

The title compound was obtained from ethyl [(4-methoxyphenyl)thio]acetate by a method similar to that of Reference Example 36. yield 91%, oil.

^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J=7.1 Hz), 3.51 (2H, s), 4.14 (2H, q, J=7.1 Hz), 6.76 (2H, d, J=8.8 Hz), 7.37 (2H, d, J=8.8 Hz).

Reference Example 41 ethyl [[4-(4-phenylbutoxy)phenyl]thio]acetate

The title compound was obtained from ethyl [(4-hydroxyphenyl)thio]acetate by a method similar to that of Reference Example 37. yield 88%, oil.

^1H NMR ($CDCl_3$) δ 1.22 (3H, t, J=7.1 Hz), 1.76-1.84 (4H, m), 2.66-2.71 (2H, m), 3.50 (2H, s), 3.93-3.97 (2H, m), 4.13 (2H, q, J=7.1 Hz), 6.82 (2H, d, J=8.8 Hz), 7.18-7.21 (3H, m), 7.26-7.29 (2H, m), 7.39 (2H, d, J=8.8 Hz).

Reference Example 42 [[4-(4-phenylbutoxy)phenyl]thio]acetic acid

The title compound was obtained from ethyl [[4-(4-phenylbutoxy)phenyl]thio]acetate by a method similar to that of Reference Example 38. yield 75%.

melting point: 73.5-74.5°C (recrystallized from ethyl acetate).

^1H NMR ($CDCl_3$) δ 1.76-1.82 (4H, m), 2.66-2.71 (2H, m), 3.55 (2H, s), 3.93-3.97 (2H, m), 6.83 (2H, d, J=8.8 Hz), 7.16-7.21 (3H, m), 7.26-7.31 (2H, m), 7.43 (2H, d, J=8.8 Hz).

Reference Example 43 methyl 4-[(2,3-dihydro-1H-inden-2-yl)oxy]benzenepropanoate

A mixture of methyl (E)-3-[4-[(2,3-dihydro-1H-inden-2-yl)oxy]phenyl]-2-propenoate (0.76 g, 2.6 mmol), tetrahydrofuran (10 mL), methanol (5 mL) and 10% palladium carbon (50% water-containing product, 0.10 g) was stirred overnight at room temperature under a hydrogen atmosphere. The reaction mixture was filtered and concentrated. Water was added, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from ethyl acetate-methanol to give the title compound (0.85 g, yield 89%).

melting point: 73-74°C.

^1H NMR ($CDCl_3$) δ 2.60 (2H, t, J=7.9 Hz), 2.90 (2H, t, J=7.9 Hz), 3.13 (1H, d, J=3.2 Hz), 3.19 (1H, d, J=3.2 Hz), 3.33 (1H, d, J=6.3 Hz), 3.38 (1H, d, J=6.3 Hz), 5.11-5.17 (1H, m), 6.84 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=6.6 Hz), 7.17-7.25 (4H, m).

Reference Example 44 4-[(2,3-dihydro-1H-inden-2-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2,3-

dihydro-1H-inden-2-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 38. yield 90%. melting point: 138-139°C (recrystallized from ethyl acetate–diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ2.66 (2H, t, J=7.9 Hz), 2.91 (2H, t, J=7.9 Hz), 3.13 (1H, d, J=3.2 Hz), 3.19 (1H, d, J=3.2 Hz), 3.33 (1H, d, J=6.3 Hz), 3.38 (1H, d, J=6.3 Hz), 5.11-5.17 (1H, m), 6.84 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=6.6 Hz), 7.16-7.25 (4H, m).

Reference Example 45 methyl 4-[(4-aminophenyl)methoxy]benzenepropanate

To a solution of methyl 4-[(4-nitrophenyl)methoxy]benzenepropanoate (0.55 g, 1.67 mmol) and bismuth (III) chloride (0.79 g, 2.5 mmol) in methanol (30 mL) was added sodium borohydride (0.51 g, 13 mmol), and the mixture was stirred at room temperature for 2 hrs. Insoluble material was filtered off, and the filtrate was concentrated. Water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogencarbonate, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=5:1) to give the title compound (0.13 g, yield 25%) as a powder.

^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J=8.0 Hz), 2.89 (2H, t, J=8.0 Hz), 3.66 (5H, br s), 4.90 (2H, s), 6.69 (2H, d, J=8.6 Hz), 6.89 (2H, d, J=8.6 Hz), 7.10 (2H, d, J=8.3 Hz), 7.21 (2H, d, J=8.3 Hz).

Reference Example 46 methyl 4-(naphthalen-2-ylmethoxy)benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and naphthalene-2-methanol by a method similar to that of Reference Example 1. yield 83%. melting point: 111-112°C (recrystallized from ethyl acetate–diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=7.4 Hz), 2.90 (2H, t, J=7.4 Hz),

3.86 (3H, s), 5.21 (2H, s), 6.94 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.47-7.55 (3H, m), 7.82-7.88 (4H, m).

Reference Example 47 4-(naphthalen-2-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-(naphthalen-2-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 38. yield 96%.
melting point: 173-174°C (recrystallized from ethyl acetate–diisopropyl ether).
^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.4 Hz), 2.91 (2H, t, J=7.4 Hz), 5.21 (2H, s), 6.94 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.47-7.55 (3H, m), 7.82-7.88 (4H, m).

Reference Example 48 methyl 4-(naphthalen-1-ylmethoxy)benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and naphthalene-1-methanol by a method similar to that of Reference Example 1. yield 84%, oil.
^{1}H NMR ($CDCl_3$) δ 2.62 (2H, t, J=7.4 Hz), 2.92 (2H, t, J=7.4 Hz), 3.68 (3H, s), 5.47 (2H, s), 6.98 (2H, d, J=8.6 Hz), 6.99 (2H, d, J=8.6 Hz), 7.44-7.60 (4H, m), 7.84-7.91 (2H, m), 8.03-8.06 (1H, m).

Reference Example 49 4-(naphthalen-1-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-(naphthalen-1-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 38. yield 81%.
melting point: 105-106°C (recrystallized from ethyl acetate–diisopropyl ether).
^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.4 Hz), 2.91 (2H, t, J=7.4 Hz), 5.44 (2H, s), 6.97 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.42-7.58 (4H, m), 7.82-7.90 (2H, m), 8.01-8.05 (1H, m).

Reference Example 50 1H-indole-2-methanol

To a mixture of indole-2-carboxylic acid (2.0 g, 12 mmol), N,N-dimethylformamide (10 mL), tetrahydrofuran (20mL) and N-

hydroxysuccinimide (1.5 g, 13 mmol) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.9 g, 15 mmol), and the mixture was stirred overnight at room temperature. 0.5 M Aqueous citric acid solution was added, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated. Tetrahydrofuran (20 mL) and sodium tetrahydroborate (1.9 g, 50 mmol) were added to the residue under ice-cooling, and the mixture was stirred at room temperature for 6 hrs. 0.5 M Aqueous citric acid solution was added, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=5:1) to give the title compound. yield 56%.

melting point: 73.5-74.4°C (recrystallized from ethyl acetate–diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ 1.79 (1H, br s), 4.83 (2H, s), 6.41 (1H, s), 7.07-7.13 (1H, m), 7.16-7.21 (1H, m), 7.34 (1H, d, J=8.3 Hz), 7.58 (1H, d, J=7.9 Hz), 8.33 (1H, br s).

Example 1 4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 33%.

melting point: 103-104°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.14-2.38 (1H, m), 2.50-2.63 (1H, m), 2.67 (2H, t, J=7.4 Hz), 2.87-2.96 (3H, m), 3.08-3.19 (1H, m), 5.73 (1H, dd, J=4.9 Hz, 6.5 Hz), 6.94 (2H, d, J=8.5 Hz), 7.15 (2H, d, J=8.5 Hz), 7.21-7.33 (3H, m), 7.42 (1H, d, J=7.2 Hz).

Example 2 4-[(1,2,3,4-tetrahydronaphthalen-1-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(1,2,3,4-tetrahydronaphthalen-1-yl)oxy]benzenepropanoate by a method

similar to that of Reference Example 4. yield 51%. melting point: 69-70°C (recrystallized from diisopropyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 1.70-1.85 (1H, m), 1.98-2.16 (3H, m), 2.74-2.89 (2H, m), 2.67 (2H, t, J=7.4 Hz), 2.93 (2H, t, J=7.4 Hz), 5.33 (1H, t, J=4.1 Hz), 6.96 (2H, d, J=8.6 Hz), 7.14-7.24 (5H, m), 7.36-7.39 (1H, m).

Example 3 4-[[2,3-dihydro-5-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[2,3-dihydro-5-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 33%. melting point: 99-100°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.15-2.30 (1H, m), 2.45-2.60 (1H, m), 2.67 (2H, t, J=7.8 Hz), 2.82-2.90 (1H, m), 2.92 (2H, t, J=7.8 Hz), 3.06-3.14 (1H, m), 5.07 (2H, s), 5.67 (1H, dd, J=6.5, 3.6 Hz), 6.85-6.93 (4H, m), 7.14 (2H, d, J=8.5 Hz), 7.30-7.44 (6H, m).

Example 4 4-[[4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from ethyl 4-[[4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 60%. melting point: 130-131°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.64 (2H, t, J=7.9 Hz), 2.90 (2H, t, J=7.9 Hz), 3.07 (3H, s), 4.78 (2H, s), 5.02 (2H, s), 6.72 (1H, s), 6.89 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.26-7.30 (1H, m), 7.34-7.41 (6H, m), 7.85-7.88 (2H, m).

Example 5 4-[(4-phenoxyphenyl)methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(4-phenoxyphenyl)methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 51%.

melting point: 144-145°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.9 Hz), 2.91 (2H, t, J=7.9 Hz), 5.00 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.00-7.03 (4H, m), 7.08-7.15 (3H, m), 7.34 (2H, t, J=8.3 Hz), 7.39 (2H, d, J=8.6 Hz).

Example 6 4-[[4-(phenylmethoxy)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained as a powder from methyl 4-[[4-(phenylmethoxy)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 11%.

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.9 Hz), 2.90 (2H, t, J=7.9 Hz), 4.96 (2H, s), 5.07 (2H, s), 6.90 (2H, d, J=8.6 Hz), 6.98 (2H, d, J=8.6 Hz) 7.12 (2H, d, J=8.6 Hz), 7.30-7.50 (7H, m).

Example 7 4-([1,1'-biphenyl]-4-ylmethoxy)benzenepropanoic acid

Methyl 4-([1,1'-biphenyl]-4-ylmethoxy)benzenepropanoate was obtained from methyl 4-hydroxybenzenepropanoate and 4-phenylbenzyl bromide by a method similar to that of Reference Example 5. This was led to the title compound by a method similar to that of Reference Example 4. yield from methyl 4-hydroxybenzenepropanoate 11%.

melting point: 187-189°C (recrystallized from tetrahydrofuran-hexane).

^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J=7.7 Hz), 2.91 (2H, t, J=7.7 Hz), 5.08 (2H, s), 6.93 (2H, d, J=8.4 Hz), 7.14 (2H, d, J=8.4 Hz), 7.30-7.50 (5H, m), 7.50-7.60 (4H, m).

Example 8 4-([1,1'-biphenyl]-3-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-([1,1'-biphenyl]-3-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 4. yield 48%.

melting point: 125-126°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.9 Hz), 2.91 (2H, t, J=7.9 Hz), 5.10 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.30-7.47 (5H, m), 7.50-7.61 (3H, m), 7.65 (1H, s).

Example 9 4-[(3-phenoxyphenyl)methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(3-phenoxyphenyl)methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 50%.

melting point: 94-95°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.64 (2H, t, J=7.9 Hz), 2.90 (2H, t, J=7.9 Hz), 5.01 (2H, s), 6.86-6.90 (2H, m), 6.88-6.98 (1H, m), 7.00-7.03 (2H, m), 7.08-7.17 (5H, m), 7.30-7.36 (3H, m).

Example 10 4-([1,1'-biphenyl]-2-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-([1,1'-biphenyl]-2-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 4. yield 45%.

melting point: 103-104°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.63 (2H, t, J=7.9 Hz), 2.88 (2H, t, J=7.9 Hz), 4.91 (2H, s), 6.79 (2H, d, J=8.6 Hz), 7.08 (2H, d, J=8.6 Hz), 7.33-7.50 (8H, m), 7.60-7.70 (1H, m).

Example 11 4-[(2-phenoxyphenyl)methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2-phenoxyphenyl)methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 45%.

melting point: 114-115°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.63 (2H, t, J=7.9 Hz), 2.89 (2H, t, J=7.9 Hz), 5.13 (2H, s), 6.86-6.92 (3H, m), 6.95-7.00 (2H, m), 7.06-7.12 (3H, m), 7.16 (1H, dd, J=7.5 Hz, 1.0 Hz), 7.24-7.36 (3H, m), 7.58 (1H, dd, J=7.5 Hz, 1.4 Hz).

Example 12 4-[(4-benzoylphenyl)methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(4-benzoylphenyl)methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 84%.

melting point: 141-142°C (recrystallized from ethyl acetate-

hexane).

^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J=8.0 Hz), 2.92 (2H, t, J=8.0 Hz), 5.14 (2H, s), 6.92 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.42-7.65 (5H, m), 7.79-7.84 (4H, m).

Example 13 4-[[4-(4-chlorobenzoyl)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[4-(4-chlorobenzoyl)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 90%.

melting point: 177-178°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J=7.9 Hz), 2.92 (2H, t, J=7.9 Hz), 5.14 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.46 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=8.2 Hz), 7.74-7.81 (4H, m).

Example 14 4-[(3-benzoylphenyl)methoxy]benzenepropanoic acid

Methyl 4-[(3-benzoylphenyl)methoxy]benzenepropanoate was obtained from methyl 4-hydroxybenzenepropanoate and 3-(bromomethyl)benzophenone by a method similar to that of Reference Example 43. Then, the title compound was obtained from methyl 4-[(3-benzoylphenyl)methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield from methyl 4-hydroxybenzenepropanoate 73%.

melting point: 84-85°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ2.65 (2H, t, J=8.0 Hz), 2.91 (2H, t, J=8.0 Hz), 5.11 (2H, s), 6.90 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.45-7.86 (9H, m).

Example 15 4-[[4-(benzoylamino)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[4-(benzoylamino)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 38. yield 42%.

melting point: 204-205°C (recrystallized from tetrahydrofuran-

hexane).
^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 2.57 (2H, t, J=8.1 Hz), 2.89 (2H, t, J=8.1 Hz), 5.02 (2H, s), 6.89 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.40-7.60 (5H, m), 7.76 (2H, d, J=8.5 Hz), 7.96-7.93 (2H, m), 9.04 (1H, s).

Example 16 methyl 4-[(4-phenoxyphenyl)methoxy]benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 4-phenoxybenzyl alcohol by a method similar to that of Reference Example 1. yield 92%.
^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.67 (3H, s), 5.00 (2H, s), 6.90 (2H, d, J=8.5 Hz), 6.97-7.03 (4H, m), 7.08-7.13 (3H, m), 7.34 (1H, t, J=7.8 Hz), 7.39 (2H, d, J=8.5 Hz).

Example 17 methyl 4-[[4-(phenylmethoxy)phenyl]methoxy]benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and 4-(benzyloxy)benzyl alcohol by a method similar to that of Reference Example 1. yield 27%, oil.
^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J=8.0 Hz), 2.89 (2H, t, J=8.0 Hz), 3.66 (3H, s), 4.96 (2H, s), 5.07 (2H, s), 6.89 (2H, d, J=8.5 Hz), 6.98 (2H, d, J=8.5 Hz) 7.11 (2H, d, J=8.5 Hz), 7.26-7.44 (7H, m).

Example 18 methyl 4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and 2,3-dihydro-1H-inden-1-ol by a method similar to that of Reference Example 1. yield 62%, oil.
^{1}H NMR ($CDCl_3$) δ 2.15-2.28 (1H, m), 2.51-2.68 (3H, m), 2.79-2.95 (3H, m), 3.07-3.23 (1H, m), 3.69 (3H, s), 5.73 (1H, dd, J=4.4 Hz, 4.8 Hz), 6.94 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz), 7.22-7.31 (3H, m), 7.42 (1H, d, J=7.2 Hz).

Example 19 methyl 4-[(1,2,3,4-tetrahydronaphthalen-1-yl)oxy]benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 1,2,3,4-tetrahydro-1-naphthol by a method similar to that of Reference Example 1. yield 63%.

^{1}H NMR ($CDCl_3$) δ 1.70-1.75 (1H, m), 1.98-2.16 (3H, m), 2.62 (2H, t, J=8.2 Hz), 2.77-2.87 (2H, m), 2.92 (2H, t, J=8.2 Hz), 3.68 (3H, s), 5.23 (1H, t, J=4.2 Hz), 6.95 (2H, d, J=8.6 Hz), 7.11-7.16 (3H, m), 7.21 (2H, dt, J=2.2 Hz, 6.8 Hz) 7.38-7.36 (1H, m).

Example 20 methyl 4-[(3-bromophenyl)methoxy]benzenepropanoate

The title compound was obtained from methyl 4-[(3-bromophenyl)methoxy]benzenepropanoate by a method similar to that of Reference Example 1. yield 68%.

^{1}H NMR ($CDCl_3$) δ2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.66 (3H, s), 5.00 (2H, s), 6.88 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.21-7.27 (1H, m), 7.34 (1H, d, J=7.5 Hz), 7.45 (1H, d, J=7.8 Hz), 7.59 (1H, s).

Example 21 4-[(3-bromophenyl)methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(3-bromophenyl)methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 43%.

melting point: 97-98°C (recrystallized from diisopropyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.8 Hz), 2.91 (2H, t, J=7.8 Hz), 5.01 (2H, s), 6.89 (2H, d, J=8.5 Hz), 7.13 (2H, d, J=8.5 Hz), 7.22-7.27 (1H, m), 7.34 (1H, d, J=7.6 Hz), 7.45 (1H, d, J=7.8 Hz), 7.59 (1H, s).

Example 22 methyl 4-([1,1'-biphenyl]-3-ylmethoxy)benzenepropanoate

Methyl 4-[(3-bromophenyl)methoxy]benzenepropanoate (0.60 g, 1.7 mmol), phenylboronic acid (0.25 g, 2.1 mmol) and sodium carbonate (0.55 g, 5.2 mmol) was dissolved in toluene-methanol-water (5:1:1, 35 mL) and, after argon substitution, tetrakistriphenylphosphinepalladium (99 mg, 0.086 mmol) was

added. The reaction mixture was heated under reflux overnight under an argon atmosphere. The reaction mixture was cooled, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=18:1) to give the title compound (0.55 g, yield 92%) as a white powder.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.66 (3H, s), 5.10 (2H, s), 6.92 (2H, d, J=8.5 Hz), 7.12 (2H, d, J=8.5 Hz), 7.35-7.47 (5H, m), 7.54-7.65 (4H, m).

Example 23 methyl 4-[(3-phenoxyphenyl)methoxy]benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and 3-phenoxybenzyl alcohol by a method similar to that of Reference Example 1. yield 66%, oil.

^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J=8.1 Hz), 2.89 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.01 (2H, s), 6.90-7.20 (9H, m), 7.20-7.36 (4H, m).

Example 24 methyl 4-([1,1'-biphenyl]-2-ylmethoxy)benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and 2-phenylbenzyl bromide by a method similar to that of Reference Example 5. yield 52%, oil.

^{1}H NMR ($CDCl_3$) δ 2.58 (2H, t, J=8.1 Hz), 2.87 (2H, t, J=8.1 Hz), 3.66 (3H, s), 4.91 (2H, s), 6.78 (2H, d, J=8.6 Hz), 7.06 (2H, d, J=8.6 Hz), 7.33-7.40 (8H, m), 7.50-7.70 (1H, m).

Example 25 methyl 4-[[2,3-dihydro-5-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 2,3-dihydro-5-(phenylmethoxy)-1H-inden-1-ol by a method similar to that of Reference Example 1. yield 65%.

^{1}H NMR ($CDCl_3$) δ 2.18-2.23 (1H, m), 2.45-2.60 (1H, m), 2.61 (2H,

t, J=8.0 Hz), 2.82-2.90 (1H, m), 2.91 (2H, t, J=8.0 Hz), 3.06-3.20 (1H, m), 3.68 (3H, s), 5.07 (2H, s), 5.67 (1H, dd, J=6.5 Hz, 3.7 Hz), 6.84-6.93 (4H, m), 7.13 (2H, d, J=8.5 Hz), 7.26-7.44 (6H, m).

Example 26 methyl 4-[(2-phenoxyphenyl)methoxy]benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 2-phenoxybenzyl alcohol by a method similar to that of Reference Example 1. yield 93%.
^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J=8.1 Hz), 2.88 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.13 (2H, s), 6.89 (3H, t, J=8.6 Hz), 6.98 (2H, d, J=8.1 Hz), 7.07-7.20 (4H, m), 7.25-7.40 (3H, m), 7.50-7.60 (1H, m).

Example 27 methyl 4-[(4-benzoylphenyl)methoxy]benzenepropanoate

To a solution of methyl 4-hydroxybenzenepropanoate (0.65 g, 3.6 mmol) in N,N-dimethylformamide (20 mL) were added 4-(bromomethyl)benzophenone (1.0 g, 3.6 mmol) and potassium carbonate (0.50 g, 3.6 mmol), and the mixture was stirred at room temperature for 15 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=9:1) to give the title compound (1.3 g, yield 96%) as a powder.
^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.67 (3H, s), 5.17 (2H, s), 6.91 (2H, d, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz), 7.46-7.60 (5H, m), 7.79-7.84 (4H, m).

Example 28 methyl 4-[[4-(4-chlorobenzoyl)phenyl]methoxy]benzenepropanoate

The title compound was obtained as a powder from methyl 4-hydroxybenzenepropanoate and [4-(bromomethyl)phenyl](4-chlorophenyl)ketone by a method similar to that of Example 27. yield 57%.

^1H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.67 (3H, s), 5.13 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.46 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=7.0 Hz), 7.74-7.80 (4H, m).

Example 29 methyl 4-[[4-(benzoylamino)phenyl]methoxy]benzenepropanoate

To a solution of methyl 4-[(4-aminophenyl)methoxy]benzenepropanoate (0.13 g, 0.44 mmol) and triethylamine (0.50 mL) in tetrahydrofuran (9 mL) was added benzoyl chloride (74 mg, 0.53 mmol), and the mixture was stirred at room temperature for 2 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=18:1) to give the title compound (0.23 g, quantitative). oil.

^1H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.67 (3H, s), 5.10 (2H, s), 6.90 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz), 7.26-7.56 (5H, m), 7.66 (2H, d, J=8.5 Hz), 7.84-7.89 (3H, m).

Example 30 methyl 4-[[4-[[methyl(4-phenyl-2-thiazolyl)amino]methyl]phenyl]methoxy]benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 4-[[methyl(4-phenyl-1,3-thiazol-2-yl)amino]methyl]benzenemethanol by a method similar to that of Reference Example 1. yield 77%.

^1H NMR ($CDCl_3$) δ 2.59 (2H, t, J=8.1 Hz), 2.89 (2H, t, J=8.1 Hz), 3.08 (3H, s), 3.66 (3H, s), 4.79 (2H, s), 5.02 (2H, s), 6.72 (1H, s), 6.89 (2H, d, J=8.6 Hz), 7.11 (2H, d, J=8.6 Hz), 7.25-7.30 (1H, m), 7.34-7.41 (6H, m), 7.86 (2H, d, J=7.1 Hz).

Example 31 methyl 4-[(2,3-dihydrobenzofuran-3-yl)oxy]benzenepropanoate

To a solution of 3-coumaranone (0.50 g, 3.7 mmol) in ethanol (20 mL) was added sodium tetrahydroborate (0.28 g, 7.5

mmol), and the mixture was stirred at room temperature for 1 hr. 0.5N Hydrochloric acid (10 mL) was added and the mixture was stirred at room temperature for 10 min. Saturated brine was added, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated. Tetrahydrofuran (10 mL), methyl 4-hydroxybenzenepropanoate (0.46 g, 2.6 mmol), triphenylphosphine (0.98 g, 3.8 mmol) and diethyl azodicarboxylate (0.91 mL, 4.7 mmol) were added to the residue, and the mixture was stirred at room temperature for 2 hrs. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=20:1) to give the title compound. yield 17%, oil.

^{1}H NMR ($CDCl_3$) δ 2.61 (2H, t, J=8.0 Hz), 2.91 (2H, t, J=8.0 Hz), 3.67 (3H, s), 4.58-4.70 (2H, m), 5.85-5.88 (1H, m), 6.85 (2H, d, J=8.6 Hz), 6.91-6.96 (2H, m), 7.14 (2H, d, J=8.6 Hz), 7.25-7.33 (1H, m), 7.38-7.40 (1H, m).

Example 32 4-[(2,3-dihydrobenzofuran-3-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2,3-dihydrobenzofuran-3-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 38. yield 60%.

melting point: 106-107°C (recrystallized from ethyl acetate–diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ 2.67 (2H, t, J=8.0 Hz), 2.93 (2H, t, J=8.0 Hz), 4.59-4.71 (2H, m), 5.86-5.89 (1H, m), 6.85 (2H, d, J=8.6 Hz), 6.91-6.96 (2H, m), 7.15 (2H, d, J=8.6 Hz), 7.26-7.33 (1H, m), 7.38-7.40 (1H, m).

Example 33 methyl 4-[(2,3-dihydro-1H-inden-1-yl)oxy]-3,5-difluorobenzenepropanoate

To a mixture of methyl (E)-3-[4-[(2,3-dihydro-1H-inden-1-yl)oxy]-3,5-difluorophenyl]-2-propenoate (0.52 g, 1.6 mmol),

samarium (1.2 g, 7.9 mmol), tetrahydrofuran (3 mL) and methanol (7 mL) was added iodine (0.80 g, 3.2 mmol), and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid (20 mL) was added and the mixture was stirred for 20 min. The mixture was diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=10:1) to give the title compound. yield 60%, oil.

^{1}H NMR ($CDCl_3$) δ 2.34-2.40 (2H, m), 2.61 (2H, t, J=7.5 Hz), 2.81-2.91 (3H, m), 3.20-3.30 (1H, m), 5.61 (1H, t, J=4.4 Hz), 6.72-6.78 (2H, m), 7.16-7.22 (1H, m), 7.29-7.31 (2H, m), 7.34 (1H, d, J=7.4 Hz).

Example 34 3,5-difluoro-4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 3,5-difluoro-4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 38. yield 75%. melting point: 88-89°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.34-2.40 (2H, m), 2.67 (2H, t, J=7.5 Hz), 2.81-2.92 (3H, m), 3.20-3.30 (1H, m), 5.62 (1H, t, J=4.4 Hz), 6.72-6.80 (2H, m), 7.17-7.23 (1H, m), 7.29-7.36 (3H, m).

Example 35 4-[[2,3-dihydro-4-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoic acid

Methyl 4-[[2,3-dihydro-4-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoate was obtained from methyl 4-hydroxybenzenepropanoate and 2,3-dihydro-4-(phenylmethoxy)-1H-inden-1-ol by a method similar to that of Reference Example 1. oil. The title compound was obtained from methyl 4-[[2,3-dihydro-4-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield from methyl 4-hydroxybenzenepropanoate 27%.

melting point: 111-111.5°C (recrystallized from diethyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ. .2.10-2.30 (1H, m), 2.50-2.60 (1H, m), 2.67 (2H, t, J=7.9 Hz), 2.40-3.00 (3H, m), 3.09-3.14 (1H, m), 5.12 (2H, s), 5.74 (1H, dd, J=6.7 Hz, 4.4 Hz), 6.85 (1H, d, J=8.0 Hz), 6.94 (2H, d, J=8.6 Hz), 7.05 (1H, d, J=7.5 Hz), 7.13-7.23 (3H, m), 7.29-7.45 (5H, m).

Example 36 methyl 4-[[2,3-dihydro-6-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and 2,3-dihydro-6-(phenylmethoxy)-1H-inden-1-ol by a method similar to that of Reference Example 1. yield 40%, oil.

^{1}H NMR ($CDCl_3$) δ 2.10-2.30 (1H, m), 2.53-2.55 (3H, m), 2.75-2.94 (3H, m), 3.01-3.10 (1H, m), 3.68 (3H, s), 5.01 (1H, d, J=11.7 Hz), 5.06 (1H, d, J=11.7 Hz), 5.68 (1H, dd, J=6.5 Hz, 4.9 Hz), 6.91-6.96 (3H, m), 7.03 (1H, d, J=1.7 Hz), 7.08-7.20 (3H, m), 7.31-7.43 (5H, m).

Example 37 4-[[2,3-dihydro-6-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[2,3-dihydro-6-(phenylmethoxy)-1H-inden-1-yl]oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 51%. melting point: 106-107°C (recrystallized from diisopropyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 2.14-2.25 (1H, m), 2.51-2.63 (1H, m), 2.67 (2H, t, 8.0 Hz), 2.79-2.95 (3H, m), 3.01-3.10 (1H, m), 5.01 (1H, d, J=11.8 Hz), 5.06 (1H, d, J=11.8 Hz), 5.69 (1H, t, J=4.8 Hz), 6.92-6.96 (3H, m), 7.05 (1H, d, J=7.9 Hz), 7.14-7.20 (3H, m), 7.20-7.43 (5H, m).

Example 38 methyl (S)-4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate

Methyl 4-hydroxybenzenepropanoate (4.1 g, 22 mmol) was dissolved in tetrahydrofuran (50 mL) and the mixture was

stirred at -30°C. (R)-1-Indanol (98% ee) (3.0 g, 22 mmol), 1,1'-(azodicarbonyl)dipiperidine (5.66 g, 22 mmol) and tributylphosphine (5.6 mL, 22 mmol) were added and the mixture was stirred at -30°C for 23 hrs. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The mixture was concentrated under reduced pressure and the obtained oil was purified by silica gel chromatography (hexane to hexane/ethyl acetate=10:1) to give the title compound (4.4 g, yield 66%) as a yellow oil.

Example 39 methyl (R)-4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate

The title compound was obtained as an oil from (S)-1-indanol and methyl 4-hydroxybenzenepropanoate by a method similar to that of Example 38. yield 70%.

Example 40 (S)-4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

(Synthetic Method 1)

4-[(2,3-Dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid (100 mg) was separated by high performance liquid chromatography (column:CHIRALCEL OJ (50 mmID×500 mm, manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.), mobile phase: hexane/ethanol/trifluoroacetic acid=90:10:0.1, flow rate: 80 mL/min, column temperature: 50°C) to give the title compound (36 mg). Optical rotation of this compound showed (+).

(Synthetic Method 2)

Methyl (S)-4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate (4.4 g, 15 mmol) was dissolved in methanol (50 mL), 1N aqueous sodium hydroxide solution (25 mL) was added and the mixture was stirred at room temperature for 18.5 hrs. 1N Hydrochloric acid (25 mL) was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over sodium

sulfate. The mixture was concentrated under reduced pressure and the obtained crystals were washed with hexane to give colorless crystals (4.2 g, 96% ee). The crystals were recrystallized from a mixed solvent of diisopropyl ether (70 mL) and hexane (70 mL) to give the title compound (2.3 g, 99.4% ee, yield 56%) as colorless crystals. As the secondary crystals, 0.67 g (yield 16%, 97% ee) of the title compound was obtained and as the tertiary crystals, 0.16 g (yield 4%, 92% ee) of the title compound was obtained.

melting point: 112-113°C (primary crystals).

$[\alpha]_D^{23}$ +28.9° (c 0.997, $CHCl_3$).

IR (KBr) ν cm^{-1}: 2938, 1694, 1510, 1232, 957, 829, 761.

^1H NMR ($CDCl_3$) δ 2.20 (1H, m), 2.55 (1H, m), 2.67 (2H, t, J=7.6 Hz), 2.92 (2H, t, J=7.6 Hz), 2.92 (1H, m), 3.13 (1H, m), 5.73 (1H, dd, J=4.4 Hz, 6.8 Hz), 6.94 (2H, dt J=2.6 Hz, 8.4 Hz), 7.16 (2H, dt, J=2.6 Hz, 8.4 Hz), 7.23 (1H, m), 7.30 (2H, m), 7.42 (1H, d, J=7.2 Hz), 11.0 (1H, br s).

Example 41 (R)-4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

(Synthetic Method 1)

4-[(2,3-Dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid (100 mg) was separated by high performance liquid chromatography (column:CHIRALCEL OJ (50 mmID×500 mm, manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.), mobile phase: hexane/ethanol/trifluoroacetic acid=90:10:0.1, flow rate: 80 mL/min, column temperature: 50°C) to give the title compound (38 mg). Optical rotation of this compound showed (-).

(Synthetic Method 2)

The title compound was obtained from methyl (R)-4-[(2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Example 40. yield: primary crystals (99.0% ee) 39%, secondary crystals (97% ee) 20%, tertiary crystals (92% ee) 7%.

melting point: 110-111°C (primary crystals).

$[\alpha]_D^{23}$ -28.8° (c 0.997, $CHCl_3$).

IR (KBr) ν cm^{-1}: 2938, 1694, 1510, 1232, 957, 829, 761.

^1H NMR ($CDCl_3$) δ 2.20 (1H, m), 2.55 (1H, m), 2.67 (2H, t, J=7.6 Hz), 2.92 (2H, t, J=7.6 Hz), 2.92 (1H, m), 3.13 (1H, m), 5.73 (1H, dd, J=4.4 Hz, 6.8 Hz), 6.94 (2H, dt J=2.6 Hz, 8.4 Hz), 7.16 (2H, dt, J=2.6 Hz, 8.4 Hz), 7.23 (1H, m), 7.30 (2H, m), 7.42 (1H, d, J=7.6 Hz), 11.0 (1H, br s).

Example 42 methyl 4-[[3-(3-thienyl)phenyl]methoxy]benzenepropanoate

Methyl 4-[(3-bromophenyl)methoxy]benzenepropanoate (0.96 g, 2.8 mmol), bis(pinacolato)diboron (0.77 g, 3.0 mmol) and potassium acetate (0.81 g, 8.3 mmol) were dissolved in N,N-dimethylformamide (30 mL) and, after argon substitution, 1,1'-bis(diphenyphosphino)ferrocenedichloropalladium (II) (0.067 g, 0.083 mmol) was added. The reaction mixture was heated overnight under an argon atmosphere at 80°C. The reaction mixture was cooled, and 3-bromothiophene (0.43 g, 2.6 mmol), 1,1'-bis(diphenyphosphino)ferrocenedichloropalladium (II) (0.067 g, 0.083 mmol) and 2N aqueous sodium carbonate solution (6.9 mL, 14 mmol) were added to the reaction mixture. The reaction mixture was heated overnight under an argon atmosphere at 80°C. The reaction mixture was cooled, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=15:1) to give the title compound (0.21 g, yield 22%) as an oil.

^1H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.66 (3H, s), 5.08 (2H, s), 6.89-6.94 (2H, m), 7.10-7.14 (2H, m), 7.33-7.44 (4H, m), 7.47 (1H, t, J=2.2 Hz), 7.55 (1H, dt, J=7.5 Hz, 1.6 Hz), 7.66 (1H, s).

Example 43 4-[[3-(3-thienyl)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[3-(3-thienyl)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 33%.
melting point: 153.0-153.5°C (recrystallized from diisopropyl ether-hexane).
^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=8.0 Hz), 2.91 (2H, t, J=8.0 Hz), 5.08 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz), 7.33-7.47 (5H, m), 7.55 (1H, dt, J=7.5 Hz, 1.5 Hz), 7.65 (1H, s).

Example 44 methyl 4-[[3-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenyl]methoxy]benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and 3-[[5-(trifluoromethyl)-2-pyridinyl]oxy]benzyl alcohol by a method similar to that of Reference Example 1. yield 89%, oil.
^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.89 (2H, t, J=8.0 Hz), 3.66 (3H, s), 5.07 (2H, s), 6.89 (2H, d, J=8.6 Hz), 7.01 (1H, d, J=8.7 Hz), 7.09-7.13 (3H, m), 7.23 (1H, br s), 7.31 (1H, d, J=7.6 Hz), 7.44 (1H, t, J=7.9 Hz), 7.90 (1H, dd, J=8.7 Hz, 2.4 Hz), 8.44 (1H, br s).

Example 45 4-[[3-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[3-[[5-(trifluoromethyl)-2-pyridinyl]oxy]phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 28%.
melting point: 112-113°C (recrystallized from diisopropyl ether-hexane).
^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 5.07 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.01 (1H, d, J=8.7 Hz), 7.09-7.17 (3H, m), 7.24 (1H, br s), 7.31 (1H, d, J=9.2 Hz), 7.44 (1H, t, J=7.9 Hz), 7.90 (1H, dd, J=8.7 Hz, 2.5 Hz), 8.44-8.45 (1H, m).

Example 46 methyl 4-[(2-methyl[1,1'-biphenyl]-3-yl)methoxy]benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and 2-methyl-3-biphenylmethanol by a method similar to that of Reference Example 1. yield 51%, white powder.

^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 2.61 (2H, t, J=8.1 Hz), 2.91 (2H, t, J=8.1 Hz), 3.67 (3H, s), 5.06 (2H, s), 6.95 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz), 7.22-7.44 (8H, m).

Example 47 4-[(2-methyl[1,1'-biphenyl]-3-yl)methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2-methyl[1,1'-biphenyl]-3-yl)methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 53%.

melting point: 154-155°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 2.66 (2H, t, J=7.9 Hz), 2.92 (2H, t, J=7.9 Hz), 5.06 (2H, s), 6.95 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.24-7.44 (8H, m).

Example 48 methyl 4-[[3-(2-thienyl)phenyl]methoxy]benzenepropanoate

The title compound was obtained as a white powder from 2-thiopheneboronic acid by a method similar to that of Example 22. yield 33%.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.1 Hz), 2.90 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.06 (2H, s), 6.92 (2H, d, J=8.6 Hz), 7.06-7.14 (3H, m), 7.28 (1H, dd, J=5.1 Hz, 1.1 Hz), 7.30-7.41 (3H, m), 7.56 (1H, dt, J=7.4 Hz, 1.6 Hz), 7.66 (1H, s).

Example 49 4-[[3-(2-thienyl)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[3-(2-thienyl)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 52%.

melting point: 127-128°C (recrystallized from ethyl acetate-

hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=8.0 Hz), 2.91 (2H, t, J=8.0 Hz), 5.07 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.08 (1H, dd, J=4.5 Hz, 3.5 Hz), 7.14 (2H, d, J=8.6 Hz), 7.27-7.41 (4H, m), 7.57 (1H, dt, J=7.4 Hz, 1.6 Hz), 7.66 (1H, s).

Example 50 methyl 4-([4'-chloro-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoate

The title compound was obtained as a oil from 4-chlorophenylboronic acid by a method similar to that of Example 22. yield 59%.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.1 Hz), 2.90 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.09 (2H, s), 6.92 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.38-7.54 (7H, m), 7.61 (1H, br s).

Example 51 4-([4'-chloro-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-([4'-chloro-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 4. yield 52%. melting point: 147-148°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.9 Hz), 2.91 (2H, t, J=7.9 Hz), 5.09 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz), 7.39-7.53 (7H, m), 7.61 (1H, s).

Example 52 methyl 4-[[3-(2-pyrimidinyl)phenyl]methoxy]benzenepropanoate

Methyl 4-[(3-bromophenyl)methoxy]benzenepropanoate (0.70 g, 2.0 mmol), bis(pinacolato)diboron (0.56 g, 2.2 mmol) and potassium acetate (0.59 g, 6.0 mmol) were dissolved in N,N-dimethylformamide (20 mL) and, after argon substitution, 1,1'-bis(diphenyphosphino)ferrocenedichloropalladium (II) (0.049 g, 0.060 mmol) was added. The reaction mixture was heated under an argon atmosphere at 80°C for 8 hrs. The reaction mixture was cooled, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was

washed with water, dried and concentrated. The residue was dissolved in toluene–methanol–water (5:1:1, 35 mL), sodium carbonate (0.64 g, 6.0 mmol) was added and, after argon substitution, tetrakistriphenylphosphinepalladium (0.12 g, 0.10 mmol) was added. The reaction mixture was heated under reflux overnight under an argon atmosphere. The reaction mixture was cooled, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=5:1) to give the title compound (0.13 g, yield 16%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J=8.1 Hz), 2.89 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.13 (2H, s), 6.92-6.94 (2H, m), 7.09-7.13 (2H, m), 7.17-7.20 (1H, m), 7.41-7.86 (2H, m), 8.41 (1H, dt, J=7.6 Hz, 1.6 Hz), 8.42-8.52 (1H, m), 8.80 (2H, d, 4.8 Hz).

Example 53 4-[[3-(2-pyrimidinyl)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[3-(2-pyrimidinyl)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 26%.

melting point: 152-153°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.9 Hz), 2.91 (2H, t, J=7.9 Hz), 5.14 (2H, s), 6.94 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.22 (1H, t, J=4.9 Hz), 7.49-7.60 (2H, m), 8.40 (1H, d, J=7.6 Hz), 8.50 (1H, s), 8.83 (2H, d, J=4.8 Hz).

Example 54 methyl 4-([4'-trifluoromethyl-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoate

The title compound was obtained as a white powder from 4-trifluoromethylphenylboronic acid by a method similar to that of Example 22. yield 82%.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.91 (2H, t, J=8.0 Hz), 3.66 (3H, s), 5.11 (2H, s), 6.93 (2H, d, J=8.7 Hz), 7.13 (2H,

d, J=8.7 Hz), 7.47-7.57 (3H, m), 7.66-7.70 (5H, m).

Example 55 4-([4'-trifluoromethyl-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-([4'-trifluoromethyl-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 4. yield 53%. melting point: 144°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.9 Hz), 2.91 (2H, t, J=7.9 Hz), 5.11 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.8 Hz), 7.47-7.56 (3H, m), 7.66-7.09 (5H, m).

Example 56 methyl 4-([2',6'-dimethyl-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoate

The title compound was obtained as a oil from 2,6-dimethylphenylboronic acid by a method similar to that of Example 22. yield 88%.

^{1}H NMR ($CDCl_3$) δ 2.01 (6H, s), 2.59 (2H, t, J=8.1 Hz), 2.89 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.09 (2H, s), 6.89 (2H, d, J=8.6 Hz), 7.09-7.20 (7H, m), 7.38-7.44 (2H, m).

Example 57 4-([2',6'-dimethyl-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-([2',6'-dimethyl-1,1'-biphenyl]-3-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 4. yield 51%. melting point: 136-137°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.00 (6H, s), 2.64 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 5.09 (2H, s), 6.90 (2H, d, J=8.6 Hz), 7.08-7.25 (7H, m), 7.35-7.50 (2H, m).

Example 58 methyl 4-[[3-(phenylmethoxy)phenyl]methoxy]benzenepropanoate

The title compound was obtained from methyl 4-hydroxybenzenepropanoate and 3-benzyloxybenzyl alcohol by a method similar to that of Reference Example 1. yield 92%.

^1H NMR ($CDCl_3$) δ 2.59 (2H, t, J=8.1 Hz), 2.89 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.01 (2H, s), 5.07 (2H, s), 6.86-6.94 (3H, m), 7.01 (1H, d, J=7.5 Hz), 7.07-7.12 (3H, m), 7.25-7.45 (6H, m).

Example 59 4-[[3-(phenylmethoxy)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[3-(phenylmethoxy)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 73%.

melting point: 107-108°C (recrystallized from ethyl acetate-hexane).

^1H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.9 Hz), 2.90 (2H, t, J=7.9 Hz), 5.01 (2H, s), 5.07 (2H, s), 6.87-6.94 (3H, m), 7.01 (1H, d, J=7.6 Hz), 7.06-7.13 (3H, m), 7.26-7.45 (6H, m).

Example 60 methyl 4-[[3-(2-pyridinyl)phenyl]methoxy]benzenepropanoate

Methyl 4-[(3-bromophenyl)methoxy]benzenepropanoate (0.70 g, 2.0 mmol) and 2-pyridyltrimethyltin (0.60 g, 2.4 mmol) were dissolved in N,N-dimethylformamide (15 mL) and, after argon substitution, dichlorobistriphenylphosphinepalladium (II) (0.10 g, 0.070 mmol) was added. The reaction mixture was heated under reflux overnight under an argon atmosphere. The reaction mixture was cooled, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=5:1) to give the title compound (0.24 g, yield 35%) as a colorless oil.

^1H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.1 Hz), 2.90 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.13 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.22-7.27 (1H, m), 7.46-7.51 (2H, m), 7.73-7.79 (2H, m), 7.93 (1H, dt, J=1.8 Hz, 5.0 Hz), 8.07 (1H, s), 8.70 (1H, dt, J=4.7 Hz, 1.4 Hz).

Example 61 4-[[3-(2-pyridinyl)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[3-(2-pyridinyl)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 57%.
melting point: 160-161°C (recrystallized from ethyl acetate-hexane).
^{1}H NMR ($CDCl_3$) δ 2.63 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 5.12 (2H, s), 6.93 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.24-7.29 (1H, m), 7.46-7.52 (2H, m), 7.71-7.81 (2H, m), 7.87-7.91 (1H, m), 8.05 (1H, s), 8.72-8.75 (1H, m).

Example 62 methyl 4-[[3-(2-naphthyl)phenyl]methoxy]benzenepropanoate

The title compound was obtained as a white powder from 2-naphthylboronic acid by a method similar to that of Example 22. yield 93%.
^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.66 (3H, s), 5.13 (2H, s), 6.94 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.42-7.53 (4H, m), 7.68 (1H, dt, J=7.4 Hz, 1.5 Hz), 7.73-7.80 (2H, m), 7.85-7.93 (3H, m), 8.05 (1H, br s).

Example 63 4-[[3-(2-naphthyl)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[3-(2-naphthyl)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 52%.
melting point: 134-135°C (recrystallized from ethyl acetate-hexane).
^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.9 Hz), 2.91 (2H, t, J=7.9 Hz), 5.13 (2H, s), 6.95 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz), 7.43-7.53 (4H, m), 7.68 (1H, dt, J=7.5 Hz, 1.5 Hz), 7.75 (1H, dd, J=8.6 Hz, 1.8 Hz), 7.78 (1H, s), 7.85-7.93 (3H, m), 8.05 (1H, br s).

Example 64 4-[[3-(5-pyrimidinyl)phenyl]methoxy]benzenepropanoic acid

Methyl 4-[(3-bromophenyl)methoxy]benzenepropanoate (0.70 g, 2.0 mmol), bis(pinacolato)diboron (0.56 g, 2.2 mmol) and

potassium acetate (0.59 g, 6.0 mmol) were dissolved in N,N-dimethylformamide (20 mL) and, after argon substitution, 1,1'-bis(diphenyphosphino)ferrocenedichloropalladium (II) (0.049 g, 0.060 mmol) was added. The reaction mixture was heated overnight under an argon atmosphere at 80°C. The reaction mixture was cooled, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was dissolved in toluene—methanol—water (5:1:1, 35 mL), sodium carbonate (0.64 g, 6.0 mmol) was added and, after argon substitution, tetrakistriphenylphosphinepalladium (0.12 g, 0.10 mmol) was added. The reaction mixture was heated under reflux overnight under an argon atmosphere. The reaction mixture was cooled, water was added and the reaction mixture was washed with ethyl acetate. Then the aqueous layer was neutralized with 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was recrystallized from tetrahydrofuran-hexane to give the title compound (0.94 g, yield 14%).

melting point: 166-167°C.

^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 2.60 (2H, t, J=8.1 Hz), 2.91 (2H, t, J=8.1 Hz), 5.13 (2H, s), 6.92 (2H, d, J=8.6 Hz), 7.16 (2H, d, J=8.6 Hz), 7.54 (3H, s), 7.65 (1H, s), 8.96 (2H, s), 9.21 (1H, s).

Example 65 methyl 4-[[4-(4-phenoxyphenoxy)phenyl]methoxy]benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 4-(4-phenoxyphenoxy)benzyl alcohol by a method similar to that of Reference Example 33. yield 26%.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.1 Hz), 2.90 (2H, t, J=8.1 Hz), 3.66 (3H, s), 4.99 (2H, s), 6.89 (2H, d, J=8.6 Hz), 6.99-7.13 (11H, m), 7.31-7.40 (4H, m).

Example 66 4-[[4-(4-phenoxyphenoxy)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[4-(4-phenoxyphenoxy)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 81%.

melting point: 167-168°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=8.0 Hz), 2.91 (2H, t, J=8.0 Hz), 4.99 (2H, s), 6.91 (2H, d, J=8.6 Hz), 6.99-7.15 (11H, m), 7.31-7.40 (4H, m).

Example 67 methyl 4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]methoxy]benzenepropanoate

4-[4-(Trifluoromethoxy)phenoxy]benzyl alcohol was obtained as an oil from 4-[4-(trifluoromethoxy)phenoxy]benzaldehyde by a method similar to that of Reference Example 32. The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 4-[4-(trifluoromethoxy)phenoxy]benzyl alcohol by a method similar to that of Reference Example 33. yield from 4-[4-(trifluoromethoxy)phenoxy]benzaldehyde 27%.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.1 Hz), 2.90 (2H, t, J=8.1 Hz), 3.67 (3H, s), 5.01 (2H, s), 6.90 (2H, d, J=6.7 Hz), 6.92-7.03 (4H, m), 7.11-7.20 (4H, m), 7.41 (2H, d, J=8.6 Hz).

Example 68 4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 87%.

melting point: 137-138°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J=8.0 Hz), 2.91 (2H, t, J=8.0 Hz), 5.01 (2H, s), 6.90 (2H, d, J=8.6 Hz), 6.99-7.03 (4H, m), 7.12-7.20 (4H, m), 7.41 (2H, d, J=8.6 Hz).

Example 69 methyl 4-[[4-([1,1'-biphenyl]-4-

yloxy)phenyl]methoxy]benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 4-([1,1'-biphenyl]-4-yloxy)benzyl alcohol by a method similar to that of Reference Example 33. yield 13%.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.90 (2H, t, J=8.0 Hz), 3.67 (3H, s), 5.01 (2H, s), 6.91 (2H, d, J=8.6 Hz), 7.05-7.14 (6H, m), 7.30-7.48 (5H, m), 7.55-7.58 (4H, m).

Example 70 4-[[4-([1,1'-biphenyl]-4-yloxy)phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[4-([1,1'-biphenyl]-4-yloxy)phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 84%.

melting point: 196-197°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J=7.9 Hz), 2.92 (2H, t, J=7.9 Hz), 5.01 (2H, s), 6.92 (2H, d, J=8.6 Hz), 7.05-7.13 (6H, m), 7.31-7.48 (5H, m), 7.55-7.58 (4H, m).

Example 71 methyl 4-[[4-[4-(phenylmethoxy)phenoxy]phenyl]methoxy]benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 4-[4-(phenylmethoxy)phenoxy]benzyl alcohol by a method similar to that of Reference Example 33. yield 24%.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.0 Hz), 2.89 (2H, t, J=8.0 Hz), 3.66 (3H, s), 4.97 (2H, s), 5.05 (2H, s), 6.88-6.97 (8H, m), 7.11 (2H, d, J=8.6 Hz), 7.34-7.47 (7H, m).

Example 72 4-[[4-[4-(phenylmethoxy)phenoxy]phenyl]methoxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[4-[4-(phenylmethoxy)phenoxy]phenyl]methoxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 55%.

melting point: 180-181°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=8.0 Hz), 2.91 (2H, t, J=8.0 Hz), 4.98 (2H, s), 5.05 (2H, s), 6.89-6.97 (8H, m), 7.13 (2H, d, J=8.6 Hz), 7.26-7.45 (7H, m).

Example 73 methyl 4-[(2,3-dihydro-5-methoxy-1H-inden-1-yl)oxy]benzenepropanoate

5-Methoxy-1-indanol was obtained from 5-methoxy-1-indanone by a method similar to that of Reference Example 32. oil. The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 5-methoxy-1-indanol by a method similar to that of Reference Example 33. yield from 5-methoxy-1-indanone 14%.

^{1}H NMR ($CDCl_3$) δ 2.19-2.29 (1H, m), 2.47-2.58 (1H, m), 2.61 (2H, t, J=8.1 Hz), 2.82-2.88 (1H, m), 2.91 (2H, t, J=8.1 Hz), 3.08-3.19 (1H, m), 3.68 (3H, s), 5.66 (1H, dd, J=3.6 Hz, 6.5 Hz), 6.78-6.82 (2H, m), 6.91 (2H, d, J=8.6 Hz), 7.12 (2H, d, J=8.6 Hz), 7.31 (1H, d, J=8.2 Hz).

Example 74 4-[(2,3-dihydro-5-methoxy-1H-inden-1-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2,3-dihydro-5-methoxy-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 67%. melting point: 87-88°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.18-2.28 (1H, m), 2.46-2.59 (1H, m), 2.67 (2H, t, J=8.0 Hz), 2.81-2.90 (1H, m), 2.92 (2H, t, J=8.0 Hz), 3.06-3.17 (1H, m), 5.68 (1H, dd, J=3.6 Hz, 6.5 Hz), 6.74-6.82 (2H, m), 6.92 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz), 7.31 (1H, d, J=8.2 Hz).

Example 75 methyl 4-[(5-chloro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate

5-Chloro-1-indanol was obtained from 5-chloro-1-indanone by a method similar to that of Reference Example 32. oil. The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 5-chloro-1-indanol by a method

similar to that of Reference Example 33. yield from 5-chloro-1-indanone 33%.

^{1}H NMR ($CDCl_3$) δ 2.16-2.27 (1H, m), 2.49-2.59 (1H, m), 2.62 (2H, t, J=8.2 Hz), 2.83-2.90 (1H, m), 2.91 (2H, t, J=8.2 Hz), 3.05-3.17 (1H, m), 3.68 (3H, s), 5.67 (1H, dd, J=4.3 Hz, 6.6 Hz), 6.91 (2H, d, J=8.6 Hz), 7.14 (2H, d, J=8.6 Hz), 7.19-7.33 (3H, m).

Example 76 4-[(5-chloro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(5-chloro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 80%.

melting point: 136-137°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.17-2.28 (1H, m), 2.51-2.62 (1H, m), 2.67 (2H, t, J=7.9 Hz), 2.85-2.90 (1H, m), 2.93 (2H, t, J=7.9 Hz), 3.06-3.17 (1H, m), 5.67 (1H, dd, J=4.4 Hz, 6.6 Hz), 6.91 (2H, d, J=8.6 Hz), 7.14-7.33 (5H, m).

Example 77 4-[(5-fluoro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

5-Fluoro-1-indanol was obtained from 5-fluoro-1-indanone by a method similar to that of Reference Example 32. oil. Methyl 4-[(5-fluoro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate was obtained from methyl 4-hydroxybenzenepropanoate and 5-fluoro-1-indanol by a method similar to that of Reference Example 33. oil. Then the title compound was obtained from methyl 4-[(5-fluoro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield from 5-fluoro-1-indanone 40%.

melting point: 124-125°C (recrystallized from diethyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 2.18-2.29 (1H, m), 2.50-2.62 (1H, m), 2.67 (2H, t, J=8.0 Hz), 2.85-2.89 (1H, m), 2.93 (2H, t, J=8.0 Hz), 3.07-3.18 (1H, m), 5.68 (1H, dd, J=4.1 Hz, 6.5 Hz), 6.90-6.98 (4H,

m), 7.15 (2H, d, J=8.6 Hz), 7.33-7.37 (1H, m).

Example 78 4-[(2,3-dihydro-5-methyl-1H-inden-1-yl)oxy]benzenepropanoic acid

5-Methyl-1-indanol was obtained from 5-methyl-1-indanone by a method similar to that of Reference Example 32. oil. Methyl 4-[(2,3-dihydro-5-methyl-1H-inden-1-yl)oxy]benzenepropanoate was obtained from methyl 4-hydroxybenzenepropanoate and 5-methyl-1-indanol by a method similar to that of Reference Example 33. oil. Then the title compound was obtained from methyl 4-[(2,3-dihydro-5-methyl-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield from 5-methyl-1-indanone 29%. melting point: 74-75°C (recrystallized from diethyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 2.13-2.25 (1H, m), 2.34 (3H, s), 2.49-2.60 (1H, m), 2.68 (2H, t, J=8.0 Hz), 2.80-2.91 (1H, m), 2.92 (2H, t, J=8.0 Hz), 3.04-3.13 (1H, m), 5.69 (1H, dd, J=4.5 Hz, 6.5 Hz), 6.94 (2H, d, J=8.6 Hz), 7.10-7.19 (4H, m), 7.24 (1H, s).

Example 79 4-[(2,3-dihydro-6-methoxy-1H-inden-1-yl)oxy]benzenepropanoic acid

6-Methoxy-1-indanol was obtained from 6-methoxy-1-indanone by a method similar to that of Reference Example 32. oil. Methyl 4-[(2,3-dihydro-6-methoxy-1H-inden-1-yl)oxy]benzenepropanoate was obtained from methyl 4-hydroxybenzenepropanoate and 6-methoxy-1-indanol by a method similar to that of Reference Example 33. oil. Then the title compound was obtained from methyl 4-[(2,3-dihydro-6-methoxy-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield from 6-methoxy-1-indanone 41%, oil.

^{1}H NMR ($CDCl_3$) δ 2.14-2.25 (1H, m), 2.51-2.63 (1H, m), 2.67 (2H, t, J=8.0 Hz), 2.79-2.88 (1H, m), 2.93 (2H, t, J=8.0 Hz), 3.01-3.09 (1H, m), 3.79 (3H, s), 5.69 (1H, dd, J=4.8 Hz, 6.5 Hz), 6.86-6.97 (4H, m), 7.13-7.20 (3H, m).

Example 80 4-[(5-bromo-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

5-Bromo-1-indanol was obtained from 5-bromo-1-indanone by a method similar to that of Reference Example 32. oil. Methyl 4-[(5-bromo-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate was obtained from methyl 4-hydroxybenzenepropanoate and 5-bromo-1-indanol by a method similar to that of Reference Example 33. oil. Then the title compound was obtained from methyl 4-[(5-bromo-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield from 5-bromo-1-indanone 29%.

melting point: 133-134°C (recrystallized from diethyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 2.15-2.27 (1H, m), 2.47-2.59 (1H, m), 2.67 (2H, t, J=8.0 Hz), 2.83-2.89 (1H, m), 2.92 (2H, t, J=8.0 Hz), 3.06-3.18 (1H, m), 5.66 (1H, dd, J=4.5 Hz, 6.5 Hz), 6.91 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.26 (1H, d, J=8.0 Hz), 7.36 (1H, d, J=8.6 Hz), 7.44 (1H, s).

Example 81 4-[(2,3-dihydro-5-phenoxy-1H-inden-1-yl)oxy]benzenepropanoic acid

5-Phenoxy-1-indanol was obtained from 5-phenoxy-1-indanone by a method similar to that of Reference Example 32. oil. Methyl 4-[(2,3-dihydro-5-phenoxy-1H-inden-1-yl)oxy]benzenepropanoate was obtained from methyl 4-hydroxybenzenepropanoate and 5-phenoxy-1-indanol by a method similar to that of Reference Example 33. oil. Then the title compound was obtained from methyl 4-[(2,3-dihydro-5-phenoxy-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield from 5-phenoxy-1-indanone 19%.

melting point: 92-93°C (recrystallized from diethyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 2.18-2.29 (1H, m), 2.50-2.61 (1H, m), 2.67 (2H, t, J=8.0 Hz), 2.81-2.90 (1H, m), 2.90 (2H, t, J=8.0 Hz), 3.05-

3.18 (1H, m), 5.70 (1H, dd, J=3.9 Hz, 6.5 Hz), 6.87-6.90 (4H, m), 7.00-7.17 (5H, m), 7.29-7.38 (3H, m).

Example 82 methyl 4-[(2,3-dihydro-4-methyl-1H-inden-1-yl)oxy]benzenepropanoate

4-Methyl-1-indanol was obtained from 4-methyl-1-indanone by a method similar to that of Reference Example 32. oil. The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 4-methyl-1-indanol by a method similar to that of Reference Example 33. yield from 4-methyl-1-indanone 4%.

^{1}H NMR ($CDCl_3$) δ 2.15-2.28 (1H, m), 2.30 (3H, s), 2.48-2.57 (1H, m), 2.62 (2H, t, J=8.1 Hz), 2.78-2.89 (1H, m), 2.91 (2H, t, J=8.1 Hz), 2.99-3.09 (1H, m), 3.68 (3H, s), 5.73 (1H, dd, J=4.1 Hz, 6.7 Hz), 6.93 (2H, d, J=8.6 Hz), 7.12-7.19 (4H, m), 7.25-7.27 (1H, m).

Example 83 4-[(2,3-dihydro-4-methyl-1H-inden-1-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2,3-dihydro-4-methyl-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 65%. melting point: 121-122°C (recrystallized from diethyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 2.16-2.27 (1H, m), 2.29 (3H, s), 2.49-2.61 (1H, m), 2.68 (2H, t, J=8.1 Hz), 2.79-2.92 (1H, m), 2.92 (2H, t, J=8.1 Hz), 3.00-3.09 (1H, m), 5.73 (1H, dd, J=4.1 Hz, 6.7 Hz), 6.94 (2H, d, J=8.6 Hz), 7.11-7.19 (4H, m), 7.25-7.27 (1H, m).

Example 84 methyl 4-[(2,3-dihydro-5,6-dimethoxy-1H-inden-1-yl)oxy]benzenepropanoate

5,6-Dimethoxy-1-indanol was obtained from 5,6-dimethoxy-1-indanone by a method similar to that of Reference Example 32. oil. Then the title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 5,6-dimethoxy-1-indanol by a method similar to that of Reference Example 33. yield from 5,6-dimethoxy-1-indanone 42%.

^{1}H NMR ($CDCl_3$) δ 2.14-2.26 (1H, m), 2.49-2.60 (1H, m), 2.62 (2H, t, J=8.2 Hz), 2.79-2.89 (1H, m), 2.91 (2H, t, J=8.2 Hz), 3.04-3.14 (1H, m), 3.68 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 5.68 (1H, dd, J=3.6 Hz, 6.6 Hz), 6.81 (1H, s), 6.91-6.94 (3H, m), 7.14 (2H, d, J=8.5 Hz).

Example 85 4-[(2,3-dihydro-5,6-dimethoxy-1H-inden-1-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2,3-dihydro-5,6-dimethoxy-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 43%. melting point: 90-92°C (recrystallized from diethyl ether-hexane).

^{1}H NMR ($CDCl_3$) δ 2.16-2.25 (1H, m), 2.49-2.61 (1H, m), 2.67 (2H, t, J=8.0 Hz), 2.80-2.91 (1H, m), 2.93 (2H, t, J=8.0 Hz), 3.04-3.15 (1H, m), 3.89 (3H, s), 3.91 (3H, s), 5.69 (1H, dd, J=3.7 Hz, 6.6 Hz), 6.80 (1H, s), 6.89-6.96 (3H, m), 7.15 (2H, d, J=8.6 Hz).

Example 86 methyl 4-[[2,3-dihydro-5-(4-methylphenyl)-1H-inden-1-yl]oxy]benzenepropanoate

5-(4-Methylphenyl)-1-indanol was obtained from 5-(4-methylphenyl)-1-indanone by a method similar to that of Reference Example 32. oil. Then the title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 5-(4-methylphenyl)-1-indanol by a method similar to that of Reference Example 33. yield from 5-(4-methylphenyl)-1-indanone 31%.

^{1}H NMR ($CDCl_3$) δ 2.21-2.32 (1H, m), 2.40 (3H, s), 2.52-2.62 (1H, m), 2.63 (2H, t, J=8.0 Hz), 2.92 (2H, t, J=8.0 Hz), 2.96-3.03 (1H, m), 3.15-3.26 (1H, m), 3.68 (3H, s), 5.76 (1H, dd, J=4.1 Hz, 6.6 Hz), 6.95 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.23-7.26 (2H, m), 7.43-7.49 (5H, m).

Example 87 4-[[2,3-dihydro-5-(4-methylphenyl)-1H-inden-1-yl]oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[2,3-

dihydro-5-(4-methylphenyl)-1H-inden-1-yl]oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 68%. melting point: 159-160°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.20-2.31 (1H, m), 2.40 (3H, s), 2.51-2.62 (1H, m), 2.68 (2H, t, J=8.0 Hz), 2.94 (2H, t, J=8.0 Hz), 2.95-3.00 (1H, m), 3.14-3.22 (1H, m), 5.76 (1H, dd, J=4.2 Hz, 6.6 Hz), 6.96 (2H, d, J=8.6 Hz), 7.16 (2H, d, J=8.6 Hz), 7.23-7.26 (2H, m), 7.43-7.50 (5H, m).

Example 88 methyl 4-[[5-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]oxy]benzenepropanoate

5-(4-Fluorophenyl)-1-indanol was obtained from 5-(4-fluorophenyl)-1-indanone by a method similar to that of Reference Example 32. oil. The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 5-(4-fluorophenyl)-1-indanol by a method similar to that of Reference Example 33. yield from 5-(4-fluorophenyl)-1-indanone 31%.

^{1}H NMR ($CDCl_3$) δ 2.19-2.31 (1H, m), 2.52-2.62 (1H, m), 2.63 (2H, t, J=8.0 Hz), 2.92 (2H, t, J=8.0 Hz), 2.94-3.01 (1H, m), 3.14-3.25 (1H, m), 3.68 (3H, s), 5.76 (1H, dd, J=4.2 Hz, 6.6 Hz), 6.95 (2H, d, J=8.6 Hz), 7.09-7.16 (4H, m), 7.38-7.55 (5H, m).

Example 89 4-[[5-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[5-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-yl]oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 86%. melting point: 169-170°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.20-2.31 (1H, m), 2.53-2.64 (1H, m), 2.68 (2H, t, J=8.0 Hz), 2.93 (2H, t, J=8.0 Hz), 2.95-3.01 (1H, m), 3.14-3.25 (1H, m), 5.77 (1H, dd, J=4.2 Hz, 6.6 Hz), 6.96 (2H, d, J=8.6 Hz), 7.09-7.18 (4H, m), 7.39-7.54 (5H, m).

Example 90 methyl 4-(dibenzo[b,d]furan-2-

ylmethoxy)benzenepropanoate

The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 2-(chloromethyl)dibenzo[b,d]furan by a method similar to that of Reference Example 5. yield 35%.

^{1}H NMR ($CDCl_3$) δ 2.60 (2H, t, J=8.1 Hz), 2.90 (2H, t, J=8.1 Hz), 3.66 (3H, s), 5.17 (2H, s), 6.94 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.32-7.58 (5H, m), 7.95 (1H, d, J=7.8 Hz), 8.02 (1H, s).

Example 91 4-(dibenzo[b,d]furan-2-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-(dibenzo[b,d]furan-2-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 4. yield 80%.

melting point: 175-176°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J=8.0 Hz), 2.92 (2H, t, J=8.0 Hz), 5.18 (2H, s), 6.94 (2H, d, J=8.6 Hz), 7.13 (2H, d, J=8.6 Hz), 7.32-7.58 (5H, m), 7.96 (1H, d, J=7.4 Hz), 8.03 (1H, s).

Example 92 methyl 4-[(2,3-dihydro-5-phenyl-1H-inden-1-yl)oxy]benzenepropanoate

5-Phenyl-1-indanol was obtained from 5-phenyl-1-indanone by a method similar to that of Reference Example 32. oil. Then the title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 5-phenyl-1-indanol by a method similar to that of Reference Example 33. yield from 5-phenyl-1-indanone 50%.

^{1}H NMR ($CDCl_3$) δ 2.20-2.31 (1H, m), 2.54-2.70 (1H, m), 2.62 (2H, t, J=8.1 Hz), 2.92 (2H, t, J=8.1 Hz), 2.98-3.04 (1H, m), 3.14-3.28 (1H, m), 3.68 (3H, s), 5.77 (1H, dd, J=4.2 Hz, 6.6 Hz), 6.95 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.32-7.60 (8H, m).

Example 93 4-[(2,3-dihydro-5-phenyl-1H-inden-1-yl)oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[(2,3-dihydro-5-phenyl-1H-inden-1-yl)oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 72%. melting point: 148-149°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.21-2.32 (1H, m), 2.55-2.75 (1H, m), 2.69 (2H, t, J=8.0 Hz), 2.94 (2H, t, J=8.0 Hz), 2.95-3.01 (1H, m), 3.16-3.25 (1H, m), 5.78 (1H, dd, J=4.2 Hz, 6.6 Hz), 6.97 (2H, d, J=8.6 Hz), 7.17 (2H, d, J=8.6 Hz), 7.32-7.60 (8H, m).

Example 94 methyl 4-[[2,3-dihydro-5-(4-methoxyphenyl)-1H-inden-1-yl]oxy]benzenepropanoate

5-(4-Methoxyphenyl)-1-indanol was obtained from 5-(4-methoxyphenyl)-1-indanone by a method similar to that of Reference Example 32. oil. The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 5-(4-methoxyphenyl)-1-indanol by a method similar to that of Reference Example 33. yield from 5-(4-methoxyphenyl)-1-indanone 38%.

^{1}H NMR ($CDCl_3$) δ 2.20-2.29 (1H, m), 2.49-2.60 (1H, m), 2.62 (2H, t, J=7.8 Hz), 2.92 (2H, t, J=7.8 Hz), 2.93-3.00 (1H, m), 3.15-3.23 (1H, m), 3.68 (3H, s), 3.85 (3H, s), 5.75 (1H, dd, J=4.1 Hz, 6.6 Hz), 6.94-6.99 (4H, m), 7.14 (2H, d, J=8.6 Hz), 7.41-7.53 (5H, m).

Example 95 4-[[2,3-dihydro-5-(4-methoxyphenyl)-1H-inden-1-yl]oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[2,3-dihydro-5-(4-methoxyphenyl)-1H-inden-1-yl]oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 94%.

melting point: 151-152°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.19-2.30 (1H, m), 2.51-2.65 (1H, m), 2.68 (2H, t, J=8.0 Hz), 2.94 (2H, t, J=8.0 Hz), 2.96-3.00 (1H, m), 3.14-3.22 (1H, m), 3.85 (3H, s), 5.70 (1H, dd, J=4.1 Hz, 6.6 Hz),

6.94-7.00 (4H, m), 7.17 (2H, d, J=8.6 Hz), 7.41-7.53 (5H, m).

Example 96 methyl 4-[[5-(4-chlorophenyl)-2,3-dihydro-1H-inden-1-yl]oxy]benzenepropanoate

5-(4-Chlorophenyl)-1-indanol was obtained from 5-(4-chlorophenyl)-1-indanone by a method similar to that of Reference Example 32. oil. The title compound was obtained as a white powder from methyl 4-hydroxybenzenepropanoate and 5-(4-chlorophenyl)-1-indanol by a method similar to that of Reference Example 33. yield from 5-(4-chlorophenyl)-1-indanone 43%.

^{1}H NMR ($CDCl_3$) δ 2.16-2.30 (1H, m), 2.50-2.56 (1H, m), 2.62 (2H, t, J=8.0 Hz), 2.92 (2H, t, J=8.0 Hz), 2.94-3.02 (1H, m), 3.14-3.23 (1H, m), 3.68 (3H, s), 5.76 (1H, dd, J=4.3 Hz, 6.5 Hz), 6.94 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.38-7.52 (7H, m).

Example 97 4-[[5-(4-chlorophenyl)-2,3-dihydro-1H-inden-1-yl]oxy]benzenepropanoic acid

The title compound was obtained from methyl 4-[[5-(4-chlorophenyl)-2,3-dihydro-1H-inden-1-yl]oxy]benzenepropanoate by a method similar to that of Reference Example 4. yield 93%. melting point: 165-166°C (recrystallized from ethyl acetate-hexane).

^{1}H NMR ($CDCl_3$) δ 2.18-2.31 (1H, m), 2.51-2.63 (1H, m), 2.68 (2H, t, J=7.8 Hz), 2.93 (2H, t, J=7.8 Hz), 2.97-3.02 (1H, m), 3.15-3.19 (1H, m), 5.77 (1H, dd, J=4.3 Hz, 6.4 Hz), 6.96 (2H, d, J=8.4 Hz), 7.17 (2H, d, J=8.4 Hz), 7.38-7.55 (7H, m).

Example 98 (+)-4-[(5-chloro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

4-[(5-Chloro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid (50 mg) was separated by high performance liquid chromatography (column:CHIRALCEL OJ (50 mmID×500 mm, manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.), mobile phase: hexane/ethanol=4:1, flow rate: 70 mL/min, column temperature: 35°C) to give the title compound (24 mg).

$[\alpha]_D^{23}$ +8.2° (c 0.45, $CHCl_3$).

Example 99 (-)-4-[(5-chloro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid

4-[(5-Chloro-2,3-dihydro-1H-inden-1-yl)oxy]benzenepropanoic acid (50 mg) was separated by high performance liquid chromatography (column:CHIRALCEL OJ (50 mmID×500 mm, manufactured by DAICEL CHEMICAL INDUSTRIES, LTD.), mobile phase: hexane/ethanol=4:1, flow rate: 70 mL/min, column temperature: 35°C) to give the title compound (23 mg).

$[\alpha]_D^{23}$ -6.2° (c 0.53, $CHCl_3$).

Example 100 methyl 4-(benzo[b]thiophen-3-ylmethoxy)benzenepropanoate

The title compound was obtained from 3-benzo[b]thiophenecarboxaldehyde and methyl 4-hydroxybenzenepropanoate by a method similar to that of Example 100. yield 79%, oil.

^{1}H NMR ($CDCl_3$) δ 2.67 (2H, t, J=7.4 Hz), 2.90 (2H, t, J=7.4 Hz), 3.69 (3H, s), 5.27 (2H, s), 6.96 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.33-7.40 (2H, m), 7.48 (1H, s), 7.80-7.90 (2H, m).

Example 101 4-(benzo[b]thiophen-3-ylmethoxy)benzenepropanoic acid

The title compound was obtained from methyl 4-(benzo[b]thiophen-3-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 38. yield 86%.

melting point: 125-126°C (recrystallized from ethyl acetate–diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.4 Hz), 2.90 (2H, t, J=7.4 Hz), 5.25 (2H, s), 6.95 (2H, d, J=8.6 Hz), 7.15 (2H, d, J=8.6 Hz), 7.30-7.40 (2H, m), 7.45 (1H, s), 7.81-7.89 (2H, m).

Example 102 methyl 4-(1H-indol-2-ylmethoxy)benzenepropanoate

The title compound was obtained from 1H-indole-2-methanol and methyl 4-hydroxybenzenepropanoate by a method similar to that of Reference Example 1. yield 12%.

melting point: 156-157°C (recrystallized from ethyl acetate–diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ 2.59 (2H, t, J=7.4 Hz), 2.89 (2H, t, J=7.4 Hz), 3.66 (3H, s), 5.21 (2H, s), 6.52 (1H, s), 6.92 (2H, d, J=8.6 Hz), 7.08-7.21 (4H, m), 7.35 (1H, d, J=7.4 Hz), 7.59 (1H, d, J=7.5 Hz), 8.33 (1H, br s).

Example 103 4-(1H-indol-2-ylmethoxy)benzenepropanoic acid

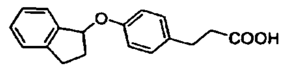
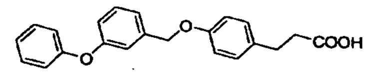
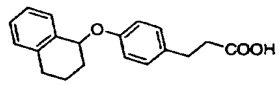
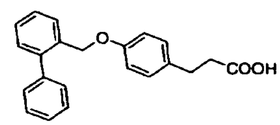
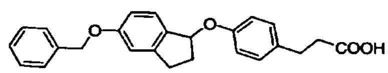
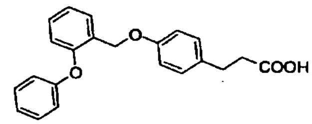
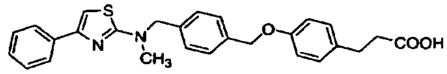
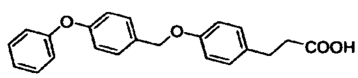
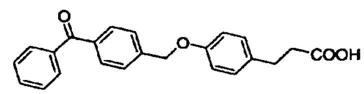
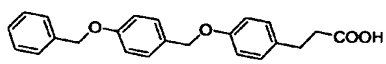
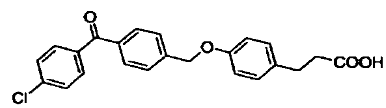
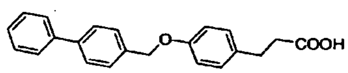
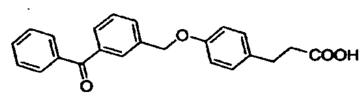
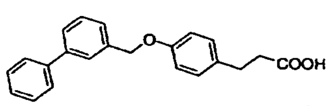
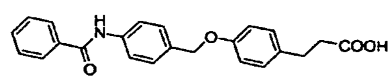
The title compound was obtained from methyl 4-(1H-indol-2-ylmethoxy)benzenepropanoate by a method similar to that of Reference Example 38. yield 53%.

melting point: 131-133°C (recrystallized from ethyl acetate–diisopropyl ether).

^{1}H NMR ($CDCl_3$) δ 2.65 (2H, t, J=7.4 Hz), 2.91 (2H, t, J=7.4 Hz), 5.21 (2H, s), 6.52 (1H, s), 6.91 (2H, d, J=8.6 Hz), 7.09-7.22 (4H, m), 7.31 (1H, d, J=7.4 Hz), 7.57 (1H, d, J=7.5 Hz), 8.33 (1H, br s).

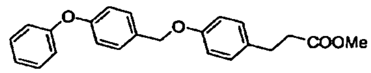
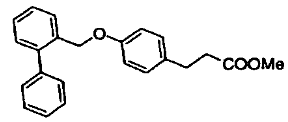
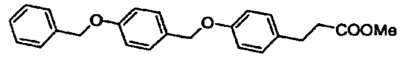
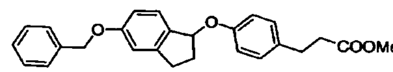
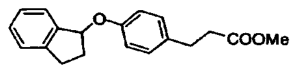
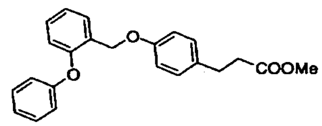
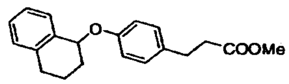
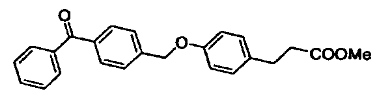
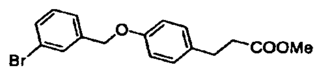
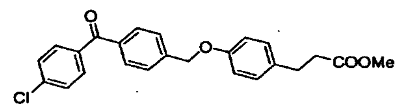
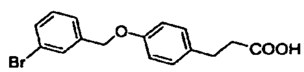
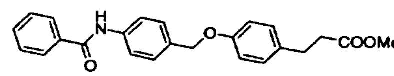
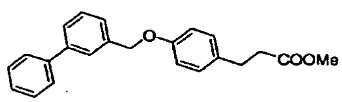
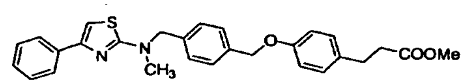
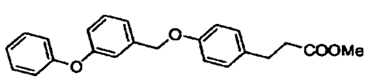
The structural formulas of the compounds obtained in Examples 1-15 are shown in Table 1.

Table 1

Example	Structure	Example	Structure
1		9	
2		10	
3		11	
4			
5		12	
6		13	
7		14	
8		15	

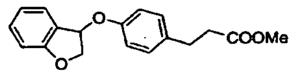
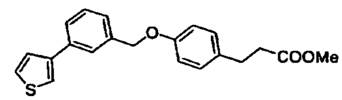
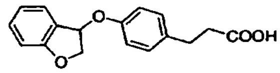
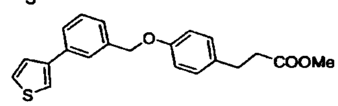
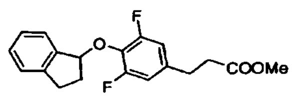
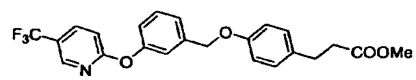
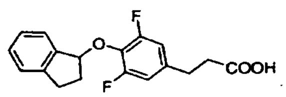
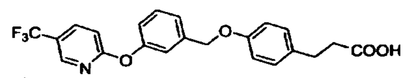
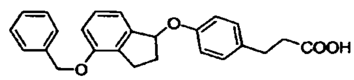
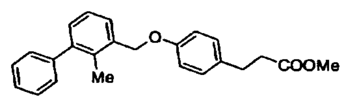
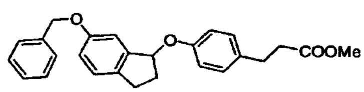
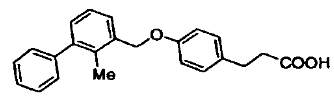
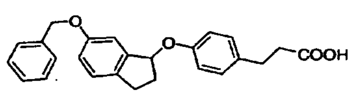
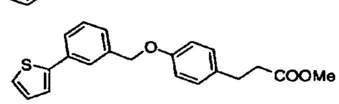
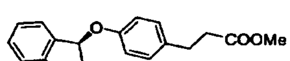
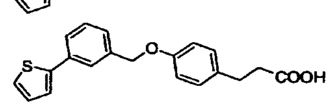
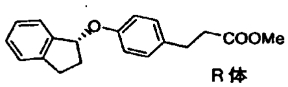
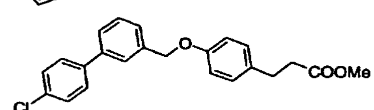
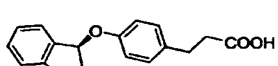
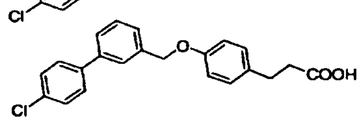
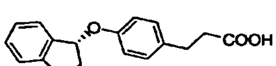
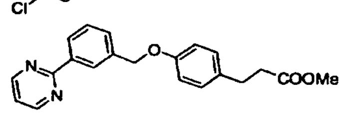
The structural formulas of the compounds obtained in Examples 16-30 are shown in Table 2.

Table 2

Example	Structure	Example	Structure
16		24	
17		25	
18		26	
19		27	
20		28	
21		29	
22		30	
23			

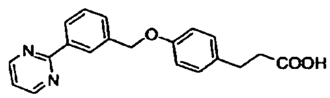
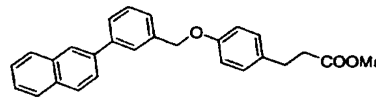
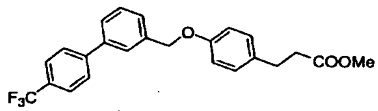
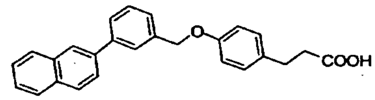
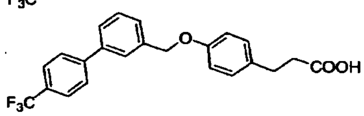
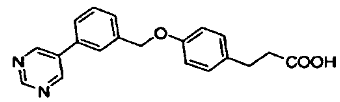
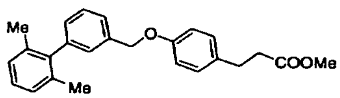
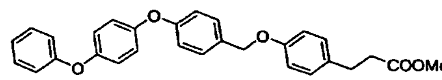
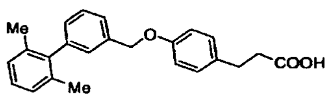
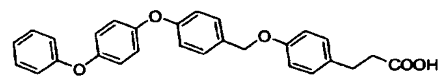
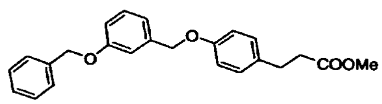
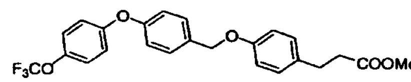
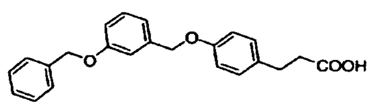
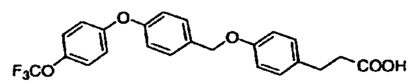
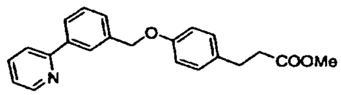
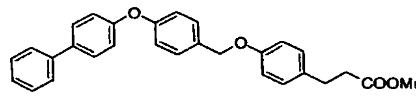
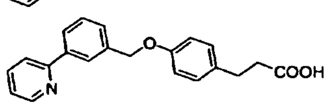
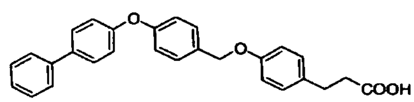
The structural formulas of the compounds obtained in Examples 31-52 are shown in Table 3.

Table 3

Example	Structure	Example	Structure
31		42	
32		43	
33		44	
34		45	
35		46	
36		47	
37		48	
38	 S体	49	
39	 R体	50	
40	 S体	51	
41	 R体	52	

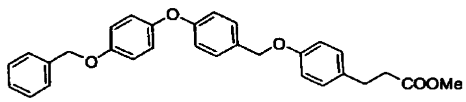
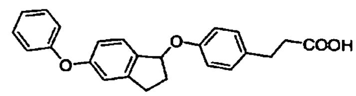
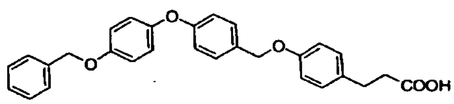
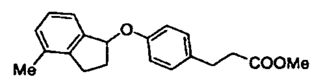
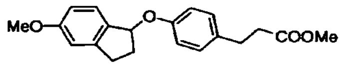
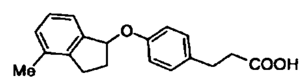
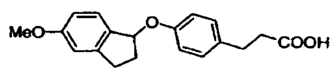
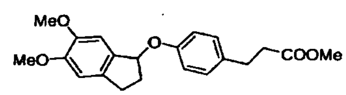
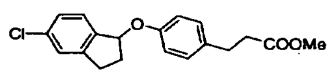
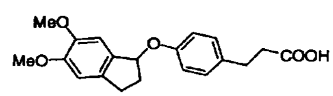
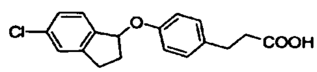
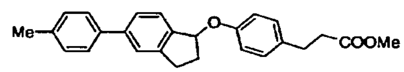
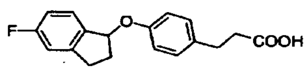
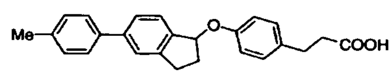
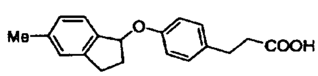
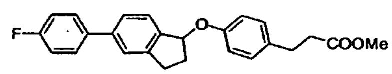
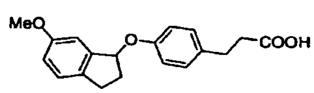
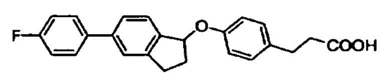
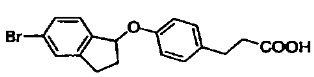
The structural formulas of the compounds obtained in Examples 53-70 are shown in Table 4.

Table 4

Example	Structure	Example	Structure
53		62	
54		63	
55		64	
56		65	
57		66	
58		67	
59		68	
60		69	
61		70	

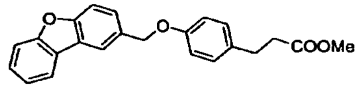
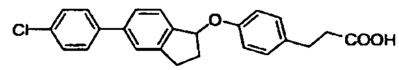
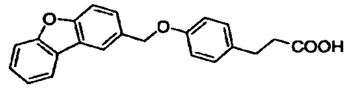
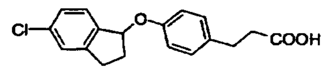
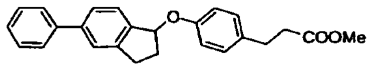
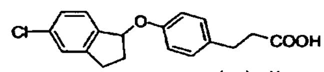
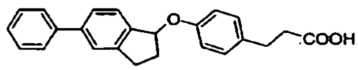
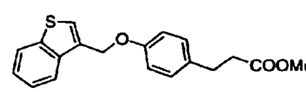
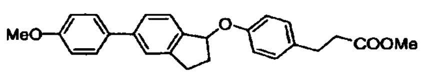
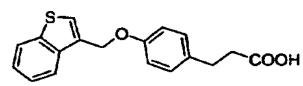
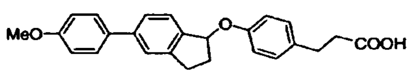
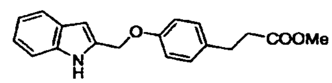
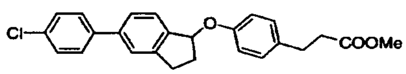
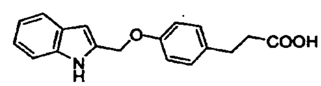
The structural formulas of the compounds obtained in Examples 71-89 are shown in Table 5.

Table 5

Example	Structure	Example	Structure
71		81	
72		82	
73		83	
74		84	
75		85	
76		86	
77		87	
78		88	
79		89	
80			

The structural formulas of the compounds obtained in Examples 90-103 are shown in Table 6.

Table 6

Example	Structure	Example	Structure
90		97	
91		98	 (+)-体
92		99	 (−)-体
93		100	
94		101	
95		102	
96		103	

Formulation Example 1

(1) Compound obtained in Example 1	10.0	g
(2) Lactose	60.0	g
(3) Cornstarch	35.0	g
(4) gelatin	3.0	g
(5) Magnesium stearate	2.0	g

A mixture of compound (10.0 g) obtained in Example 1, lactose (60.0 g) and cornstarch (35.0 g) was granulated with an aqueous solution (30 mL) of 10 wt% gelatin (3.0 g as gelatin) by passing through a 1 mm mesh sieve, dried at 40°C and passing through the sieve again. The obtained granule was mixed with magnesium stearate (2.0 g) and the mixture was compressed. The obtained core tablets were coated with glycocalyx of an aqueous suspension of saccharose, titanium dioxide, talc and gum arabic. The tablets after coating were polished with bee wax to give 1000 coated tablets.

Formulation Example 2

(1) Compound obtained in Example 1	10.0	g
(2) lactose	70.0	g
(3) cornstarch	50.0	g
(4) soluble starch	7.0	g
(5) magnesium stearate	3.0	g

The compound (10.0 g) obtained in Example 1 and magnesium stearate (3.0 g) were granulated with an aqueous solution (70 mL) of soluble starch (7.0 g as soluble starch), dried, and mixed with lactose (70.0 g) and cornstarch (50.0 g). The mixture was compressed to give 1000 tablets.

Experimental Example 1 Confirmation of reactivity of fatty acid to human-derived GPR40

Unless specifically indicated, CHO-K1 cell line was cultured using Ham's F-12 medium (Invitrogen) containing 10% fetal calf serum (Invitrogen). The day before transfection, 4.5×10^5 per 10 cm^2 of cells were seeded, and incubated at 37°C for not less than 15 hrs in a CO_2 incubator adjusted to 5% CO_2

concentration. The transfection was performed using a lipofectamine reagent (Invitrogen) and according to the reagent attached method. When a 6-well plate was used for a culture plate, transfection was performed in the following manner. First two 1.5 ml volume tubes were prepared, and 100 μl of Opti-MEM-I medium (Invitrogen) was dispensed. Then, 1 μg of an expression vector was added to one tube and 6 μl of a lipofectamine reagent was added to the other tube. They were mixed and stood still at room temperature for 20 min. A mixed solution for transfection containing this solution and Opti-MEM-I medium (800 μl) was added to CHO-K1 cell previously washed with Opti-MEM-I medium, and incubated in a CO_2 incubator for 6 hrs. The incubated cells were rinsed with PBS (Invitrogen), detached with 0.05% trypsin-EDTA solution (Invitrogen), recovered by centrifugation. The obtained cells were counted, diluted such that 5×10^4 cells were contained per 200 μl of the medium, dispensed to black walled 96-well plate (Costar) at 200 μl per well, incubated overnight in a CO_2 incubator. Various test samples were added to CHO-K1 cells transiently expressing the receptor by the above-mentioned transfection step, and changes in the intracellular calcium concentration then was measured using FLIPR (Molecular Device).

For measurement of changes in intracellular calcium concentration by FLIPR, the following pretreatment was applied. First, an assay buffer for adding fluorescence dye Fluo-3AM (DOJIN) to the cell, or washing the cell immediately before FLIPR assay was prepared. To a solution (hereinafter HBSS/HEPES solution) obtained by adding 20 ml of 1M HEPES (pH 7.4) (DOJIN) to 1000 ml of HBSS (Invitrogen) was added a solution (10 ml) obtained by dissolving probenecid (710 mg, Sigma) in 1N NaOH (5 ml) and adding and mixing with HBSS/HEPES solution (5 ml) and the obtained solution was used as an assay buffer. Then, Fluo-3AM (50 μg) was dissolved in 21 μl of DMSO (DOJIN), and an equal amount of 20% pluronic acid (Molecular

Probes) was added. The mixture was added to an assay buffer (10.6 ml) supplemented with 105 μl of fetal calf serum to give a fluorescence dye solution. The medium of the CHO-K1 cell after transfection treatment was removed, a fluorescence dye solution was immediately dispensed at 100 μl per well and incubated in a CO_2 incubator for 1 hr to incorporate the fluorescence dye into the cell. The incubated cells were washed with the above-mentioned assay buffer and set on FLIPR. The test sample to be added to receptor expressing CHO-K1 cell was prepared using the assay buffer and simultaneously set on FLIPR. After the above-mentioned pretreatment, changes in the intracellular calcium concentration after addition of various test samples were measured by FLIPR. As a result, it was found that CHO-K1 cell that expresses the GPR40 receptor specifically responds (increase in intracellular calcium concentration) when farnesoic acid, 5.8.11-eicosatriynoic acid, 5.8.11.14-eicosatetraynoic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, eicosapentaenoic acid (EPA), eicosadienoic acid, eicosatrienoic acid, docosahexaenoic acid (DHA), docosatrienoic acid, adrenic acid, lauric acid and the like are added at 10^{-5}M - 10^{-6}M. CHO-K1 cell into which only the control expression vector alone was introduced did not show such response. In other words, it was clarified that an endogenous ligand of GPR40 was fatty acid.

Experimental Example 2 Expression distribution

(1) Cell and medium

NIH-3T3 and B104 cells were purchased from the ATCC. As mouse pancreatic β cell line, MIN6 described in a literature (Jun-ichi Miyazaki et al. Endocrinology, Vol. 127, No. 1, p126-132) was used. Respective cells were incubated in DMEM medium (Invitrogen) containing 10% FCS to preconfluent.

(2) Extraction of RNA and cDNA synthesis

The cDNA used for the expression distribution in human and mouse tissues was obtained by reverse transcription

reaction from polyA+RNA (1 μg, Clontech) derived from various tissues of human and mouse using random primer. Using reverse transcriptase SuperScriptII (GIBCO BRL), the reaction was carried out according to the attached protocol and ethanol precipitation was performed and the precipitate was dissolved in TE (100 μl).

As to cDNA from the mouse cell, the cells were detached with Trypsin-EDTA, the number of the cells was counted, and the total RNA was extracted and purified according to the manual of RNeasy mini KIT (QIAGEN). The extracted RNA (1 μg) was processed according to the manual of SuperScript II (Invitrogen) using random to synthesize a first strand cDNA, which was subjected to ethanol precipitation, and the precipitate was dissolved in TE (10 μl).

(3) Quantitation using TaqMan

The tissue-derived cDNA (corresponding to 5 ng of RNA) and cell line-derived cDNA (corresponding to 25 ng of RNA) were adjusted to the total reaction mixture of 15 μl with amplification reaction reagent TaqMan (trademark) Universal PCR Master Mix (Applied Biosystems Japan Ltd.) and TaqMan (trademark) Probe Kit for GPR40 detection (sequence: 11-16, Applied Biosystems Japan Ltd.), and the reaction was carried out. The final concentration of each primer and probe followed the manual.

TaqMan (trademark) PCR was performed in ABI PRISM (trademark) 7900HT sequence detection system (Applied Biosystems Japan Ltd.), and the temperature cycle used followed the manual of TaqMan (trademark) Universal PCR Master Mix (Applied Biosystems Japan Ltd.).

The quantitative TaqMan analysis of the amplified product was performed using 7900HT SDS software (Applied Biosystems Japan Ltd.). The analytical curve used for the calculation of copy number was formed from C_T values at 6 points in the logarithm from 10^7 copies/well to 10^2 copies/well using a

concentration-known cDNA fragment (human GPR40) or Plasmid DNA (mouse GPR40) containing full length amplified region.

In human tissues, relatively high expression was observed in pancreas, lung, hippocampus, hypothalamus and spinal cord. In mouse, extremely high expression was observed in pancreatic cancer-derived cell.

Experimental Example 3 Insulin secretagogue effect of free fatty acid in mouse insulinoma MIN6 cell

Unless otherwise specified, MIN6 cell was incubated in DMEM (high glucose, Invitrogen) containing 15% FCS (Trace Scientific Ltd.), 55 μM 2-mercaptoethanol, 100 U/ml penicillin, and 100 μg/ml streptomycin. Min6 cells were seeded in a 96 well plate at 10^5 cells per well, and incubated at 37°C for 3 days in a CO_2 incubator adjusted to 5% CO_2 concentration. The medium was exchanged to RPMI1640 (glucose-free, Invitrogen) containing 10% FCS (Trace Scientific Ltd.), 5.5 mM glucose, 100 U/ml penicillin and 100 μg/ml streptomycin and the cells were further incubated for 24 hrs. The medium was aspirated, free fatty acid-bovine serum albumin (BSA) mixed solution (4:1, molar ratio) diluted with RPMI1640 (glucose-free, Invitrogen) containing 10% FCS (Trace Scientific Ltd.), 11 mM glucose, 100 U/ml penicillin, and 100 μg/ml streptomycin was added to the cells and reacted at 37°C for 90 min. (or 60 min.) in a CO_2 incubator adjusted to 5% CO_2 concentration. The 96 well plate after reaction was centrifuged at 1500 rpm for 5 min. and the culture supernatant was recovered. The insulin amount secreted in this culture supernatant liquid was determined by radioimmunoassay (RIA) using a rat insulin RIA system (Amersham Pharmacia Biotech). As a result, it was found that the insulin secretion by Min6 cell was promoted when 300 μM-1000 μM of free fatty acid such as palmitic acid, γ-linolenic acid, oleic acid and the like was added. That is, it was clarified that the free fatty acid promotes insulin secretion in mouse insulinoma MIN6 cell. Since MIN6 cell specifically

and extremely highly expresses GPR40, it is considered that the added fatty acid insulin promotes secretion via GPR40.

Experimental Example 4 Effect of regulation of GPR40 receptor function (agonistic effect)

CHO cell line (No.104) made to express human GPR40 was diluted such that 3×10^4 cells/100 μL were contained, dispensed to a black walled 96-well plate (Costar) at 100 μL per well, and incubated overnight in a CO_2 incubator. The changes in the intracellular calcium concentration were measured using FLIPR (Molecular Device). The method is described in the following.

Fluo-3AM (DOJIN) (50 μg) was dissolved in 21 μl DMSO (DOJIN), and an equal amount of 20% pluronic acid (Molecular Probes) was added and mixed, and the mixture was added to 10.6 ml of an assay buffer [prepared by adding 20 ml of 1M HEPES (pH 7.4) (DOJIN) to 1 L of HBSS (Invitrogen), and adding a mixed solution (10 ml) obtained by dissolving probenecid (Sigma) (710 mg) in 1N NaOH (5 ml) and adding and mixing with the above-mentioned HBSS/HEPES solution (5 ml)] supplemented with 105 μl of fetal calf serum to give a fluorescence dye solution. The medium in the cell plate was removed, a fluorescence dye solution was immediately dispensed at 100 μl per well, and incubated in a CO_2 incubator for 1 hr to incorporate fluorescence dye into the cell. The incubated cells were washed with the above-mentioned assay buffer. The compound to be added to the cell was diluted with the assay buffer to each concentration and dispensed to a test sample plate. After the above-mentioned pretreatment, changes in the intracellular calcium concentration after addition of the compound was measured by FLIPR, and the agonistic effect was examined. EC_{50} value was calculated from a dose response curve based on the changes in the fluorescence intensity value at 30 sec after the start of the reaction.

Table 7

Effect of regulation of GPR40 receptor function

compound No.	EC_{50} (μM)
Reference Example 2	0.32
Reference Example 6	0.46
Reference Example 15	1.2
Example 2	0.17
Example 6	0.16
Example 7	0.13
Example 10	0.88
γ.linolenic acid	2.0

From the results of Table 7 it was found that the compound of the present invention has the superior effect of regulation of GPR40 receptor function.

【Effect of the Invention】

The compound and a prodrug thereof of the present invention have superior GPR40 receptor function regulating action and can be used as agents for the prophylaxis or treatment of diabetes and the like.

【Document】 Abstract

【Summary】

【Problem】 Provision of a GPR40 receptor function regulator

【Solving Means】 A GPR40 receptor function regulator comprising a compound having an aromatic ring and a group capable of releasing cation.

【Main Drawing】 None